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SPECIAL ARTICLE

Thyroid dysfunction in the era of precision medicine

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Abstract The launching of the *Precision Medicine Initiative* by the President of the United States in January 2015 was an invitation for all healthcare professionals to review their practice. This call should stimulate thyroidologists working in different areas (from basic research or epidemiology to the frontline of the clinical arena or to those designing public health programs) to be aware of this new outlook. The aim of the initiative is to eradicate imprecision in estimating the probability of a correct diagnosis, to be as sure as possible of the most effective treatment, and to maximize the chances of a successful outcome. This paper summarizes some of the current challenges faced by endocrinologists in the field of thyroid dysfunction, and illustrates how precision medicine may improve diagnosis and therapy in the future.

PALABRAS CLAVE
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Hipertiroidismo;
Hipotiroidismo;
Disfunción tiroidea

La disfunción tiroidea en la era de la medicina de precisión

Resumen El lanzamiento de la iniciativa medicina de precisión *(Precision Medicine Initiative)*, en enero de 2015, por el Presidente de los Estados Unidos, ha supuesto una invitación a todos los profesionales sanitarios para revisar su modo de actuar. Esta llamada debe estimular a los tiroidólogos que trabajan en todos los campos (desde la investigación básica o la epidemiología, hasta aquellos que se encuentran en la primera línea del quehacer clínico o los que diseñan programas de salud pública), para estar atentos a este nuevo panorama. El objetivo de la iniciativa es erradicar la imprecisión a la hora de estimar la probabilidad de un diagnóstico correcto o tener la mayor certeza posible sobre la terapia más eficaz, y ampliar las posibilidades

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de un resultado exitoso. Este trabajo resume algunos de los desafíos actuales con los que nos enfrentamos los endocrinólogos en el campo de la disfunción tiroidea, e ilustra modos de cómo la medicina de precisión puede mejorar el diagnóstico y el tratamiento en el futuro.

Introduction

History shows that there has been continuous progress in medical science over the centuries. In recent years, a number of factors have led to the pace of this knowledge to increase from arithmetical to geometrical proportions. The list of explanatory factors is broad, including more accurate clinical assessments, a better understanding of cellular reactions and environmental influences. The more precise methods for molecular characterization of patients such as the continuous increasing number of 'omics': (proteomics, metabolomics, genomics, etc.), together with the integration of all science, the rapid interchange of knowledge among researchers, the immense possibilities of informatics in the analysis of large databases, and the growing world of robotics and artificial intelligence are among the major factors for this remarkable progress.

However, despite the availability of all these marvelous tools, the approach to prevention, diagnosis and treatment of many conditions is currently still very often based on probabilities. Frequently we offer our patients an estimation of the chance to be diagnosed or cured from a particular disease. Our knowledge of the biological variability (due to many known and even more unknown influences) still prevents us to be more accurate and precise.

In this scenario, the launching of the *Precision Medicine Initiative* by the President of the United States in January 2015 has come just at the right moment.[1] The *Initiative* has two main components to help to eradicate imprecision, with a near term focus on cancer, and a longer term focus on healthcare in general. These aims will permit better evaluation of disease risk, an understanding of their mechanisms, and prediction of the best treatments. Precision medicine has been defined as ''treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations''.[2] But, as a whole, it covers a much broader spectrum.

The benefits of precision medicine should apply to all human disease. Although most thyroid diseases are usually easily diagnosed and fully treatable, there are still ways in which the thyroid health of our patients can be improved. Table 1 summarizes some of the current challenges diagnosing and treating diseases related to thyroid function, excluding thyroid neoplastic disease.

Precision medicine in thyroid dysfunction

The future application of precision medicine in thyroid dysfunction implies the development of new approaches for detecting, measuring, and analyzing a wide range of biomedical information. A better understanding of the genetic and environmental determinants of the diverse forms of thyroid dysfunction will improve our ability to assess disease susceptibility and identify risk factors. This improved knowledge will provide means to better diagnose thyroid dysfunction more accurately, and use more individualized targeted therapies, reducing side effects and making patient monitoring more precise.

Precision in diagnosis of thyroid dysfunction

Over the past few years there has been a considerable effort to be more accurate in the biochemical diagnosis of thyroid dysfunction. In addition to the phenotypical differences (such as age, gender, weight, race, etc.), genetic factors may be responsible, at least in part, for the variability of thyrotropin (TSH) and thyroid hormone serum concentrations.[3] Some recent observations, such as the association between the nuclear factor kappa B (NFkB) and the angiotensin converting enzyme (ACE) gene polymorphisms with thyroid hormone levels,[4] indicate how complex the analysis of all the causal factors in a given individual could be.

TSH

Serum TSH measurement is the cornerstone in the diagnosis of thyroid dysfunction.[5] Unfortunately there are a number of issues in the assessment of circulating TSH[6–28] (Table 2). The numerous potential causes of assay interference illustrate the importance of a close collaboration between clinicians and the clinical chemistry laboratory staff, to avoid unnecessary testing and inappropriate treatments. Current third generation TSH assays have greatly minimized, but have not eliminated, the potential for assay interference.[29,30]

A recent meta-analysis has identified some TSH-associated loci that contribute not only to TSH variation within the normal range, but also to TSH values outside the reference range that can masquerade as thyroid dysfunction. Overall, the results of this study explain, respectively, 5.6% and 2.30% of total TSH and FT4 trait variance,[31] and such findings may have consequences for personalized decisions in treating hypothyroidism or hyperthyroidism. Although not in use at present, it is possible that genetic studies of TSH variances might be utilized in the interpretation of laboratory data in patients with thyroid dysfunction. However, the percentages of variance for TSH and FT4 are too low for precision medicine, indicating that we are currently too far away to be able to achieve accurate results with the present genetic information. In order to be more precise in the future, we will need additional information that takes into account fundamental knowledge of common vs. rare variants of the TSH gene, epigenetics, and gene-environment interactions.