

Special Article

Updating Allergy and/or Hypersensitivity Diagnostic Procedures in the WHO ICD-11 Revision

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The classification of allergy and/or hypersensitivity conditions for the World Health Organization (WHO) International Classification of Diseases (ICD)-11 provides the appropriate corresponding codes for allergic diseases, assuming that the final diagnosis is correct. This classification should be linked to *in vitro* and *in vivo* diagnostic procedures. Considering the impact for our specialty, we decided to review the codification of these procedures into the ICD aiming to have a baseline and to suggest changes and/or submit new proposals. For that, we prepared a list of the relevant allergy and/or hypersensitivity diagnostic procedures that health care professionals are dealing with on a daily basis. This was based on the main current guidelines and selected all possible and relevant corresponding terms from the ICD-10 (2015 version) and the ICD-11 β phase foundation (June 2015 version). More than 90% of very specific and important diagnostic procedures currently used by the allergists' community on a daily basis are missing. We observed that some concepts usually used by the allergist community on a

daily basis are not fully recognized by other specialties. The whole scheme and the correspondence in the ICD-10 (2015 version) and ICD-11 foundation (June 2015 version) provided us a big picture of the missing or imprecise terms and how they are scattered in the current ICD-11 framework, allowing us to submit new proposals to increase the visibility of the allergy and/or hypersensitivity conditions and diagnostic procedures. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

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ALLERGY AND/OR HYPERSENSITIVITY DIAGNOSTIC PROCEDURES

Allergy and hypersensitivity conditions are common and multidimensional problems seen by many specialties. The clinical presentation of these conditions is often complex, covering many different entities such as asthma; rhinitis; anaphylaxis; drug, food, and insect hypersensitivity; eczema; urticaria; and angioedema. However, the complexity of allergic and hypersensitivity conditions is not only limited to the clinical presentation itself, but also to their chronology, underlining pathophysiological mechanisms, triggers, and cofactors covering a myriad of conditions with variable severity and significant impact on patients' quality of life and health care costs to both patients and payers.

In a view of this multifaceted issue, it is important to stress the need for a careful clinical history associated with clinical manifestations and appropriate *in vivo* and/or *in vitro* investigation procedures.

The main *in vivo* tests currently used to investigate allergic and hypersensitivity conditions are the skin tests and the provocation tests. These procedures follow standard methods and practice parameters.¹⁻³⁴ In general, the provocation tests are considered "gold standards" and often follow a negative skin test and/or *in vitro* test. *In vivo* procedures aim to confirm the diagnosis and/or provide safe alternatives to appropriately assess allergic conditions, but are not indicated as screening tools for the general population and must be carefully interpreted. The indications for performing the different procedures depend on the suspected pathological mechanism (Table I).

The *in vivo* allergy skin tests, such as skin prick test (SPT), intradermal test (IDT), and skin patch test (PT), have been in use in the allergy field for more than 100 years. Their value as diagnostic tools is recognized worldwide and new guidelines have updated their appropriate use.¹⁻³⁴ Skin tests usually confirm sensitization to an allergen, meaning the presence of specific

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TABLE I. Main current diagnostic procedures for allergy and/or hypersensitivity

IgE-mediated hypersensitivity diagnostic procedures	T-Lymphocyte-mediated hypersensitivity diagnostic procedures
<i>In vitro</i>	<i>In vitro</i>
• Serum allergen-specific IgE • Serum (or plasma) tryptase • Basophil activation test (BAT) • Cellular Antigen Stimulation Test (CAST)-Enzyme linked ImmunoSorbent Assay (ELISA)	• Lymphocyte transformation blood test • Enzyme-Linked ImmunoSpot (ELISPOT) • Cluster of Differentiation 69 (CD69) expression
<i>In vivo</i>	<i>In vivo</i>
• Skin tests • Skin prick tests • Intradermal skin tests • Provocation test	• Skin tests • Skin patch tests and/or photopatch tests • Intradermal skin tests • Provocation test

immunoglobulin (Ig)E or T lymphocyte to an allergen in a previously exposed and sensitized patient. Skin tests help confirm the diagnosis of allergy when associated with a compatible history. The sensitivity and specificity vary according to the substance tested, the type of the test, the previous reaction, and the timing in which the patient is tested. The SPT and IDT are particularly important to demonstrate an IgE-dependent (type I mechanism) sensitization. The SPT is the initial screening test, and, generally speaking, the IDT is undertaken when the SPT is negative. To demonstrate T-lymphocyte sensitization (type IV mechanism), the PT and/or the IDT with late reading are indicated.

Regardless of the method (double-blind placebo-controlled, single-blinded placebo-controlled, or open), the substance tested (drug, food, or inhaled allergen), or the route (orally, intravenously, nasal, bronchial, or conjunctival), the provocation tests, also known as challenge tests, are considered the gold standard of *in vivo* procedures. These tests should be performed in a safe setting and must be indicated, supervised, and interpreted by an allergist. They are usually indicated (i) to confirm diagnosis, (ii) to provide a safe alternative (eg, drug challenges), (iii) to follow up previous diagnosis of allergy, and (iv) as a pharmacological model to test new compounds for treatment.

Most of the biological *in vitro* tests are usually used to prove allergic sensitization by the presence of allergen-specific IgE or allergen-specific memory lymphocytes. The demonstration of sensitization is, however, not sufficient to prove allergy. Advances in technology supported by new knowledge in pathological mechanisms have provided new laboratory tools to assist in the investigation of allergy and hypersensitivity conditions. *In vitro* tests are nowadays of great interest due to their safety for patients, reducing the need of some *in vivo* procedures sometimes associated with patient risk. However, most of the new methods still require validation to assure sensitivity and specificity.

Importantly, diagnostic procedures, both *in vivo* and *in vitro*, are utilized for better allocation of resources in both public and private health systems. The current network models of the different levels of health care systems and services related to the diagnosis, management, treatment, and generated costs are based

on encoding specific terminologies. In this context, the International Classification of Diseases (ICD) acts as a protagonist in the health communication system scenario, being now responsible for approximately 70% of the world's health expenditures.³⁵ Because the ICD codes permit the tracking of many diagnoses and support medical decision making, changes in the ICD framework can have a huge economic impact.

ALLERGY AND/OR HYPERSENSITIVITY DIAGNOSTIC PROCEDURES IN THE ICD

ICD-11 revision: an opportunity to update allergy and/or hypersensitivity conditions

The ICD is an official classification produced and owned by the World Health Organization (WHO). More than 100 years from the first ICD revision, this classification has been recognized as a global standard information system used by more than 100 countries worldwide as a diagnostic tool for epidemiology, health management, and clinical purposes. From the international perspective, its original use was for reporting mortality data (eg, cause of deaths), but has developed over the years to also be a tool for reporting morbidity. Countries reporting mortality and morbidity data to the WHO are supposed to do so in the current version of the ICD. This international complex system is, therefore, designed to map health conditions to corresponding generic categories together with specific variations, using a designated code. It is revised periodically, approximately every 10 years. It is increasingly used in clinical care and research to define diseases and study disease patterns as well as to manage health care, monitor morbidity outcomes, and allocate resources.

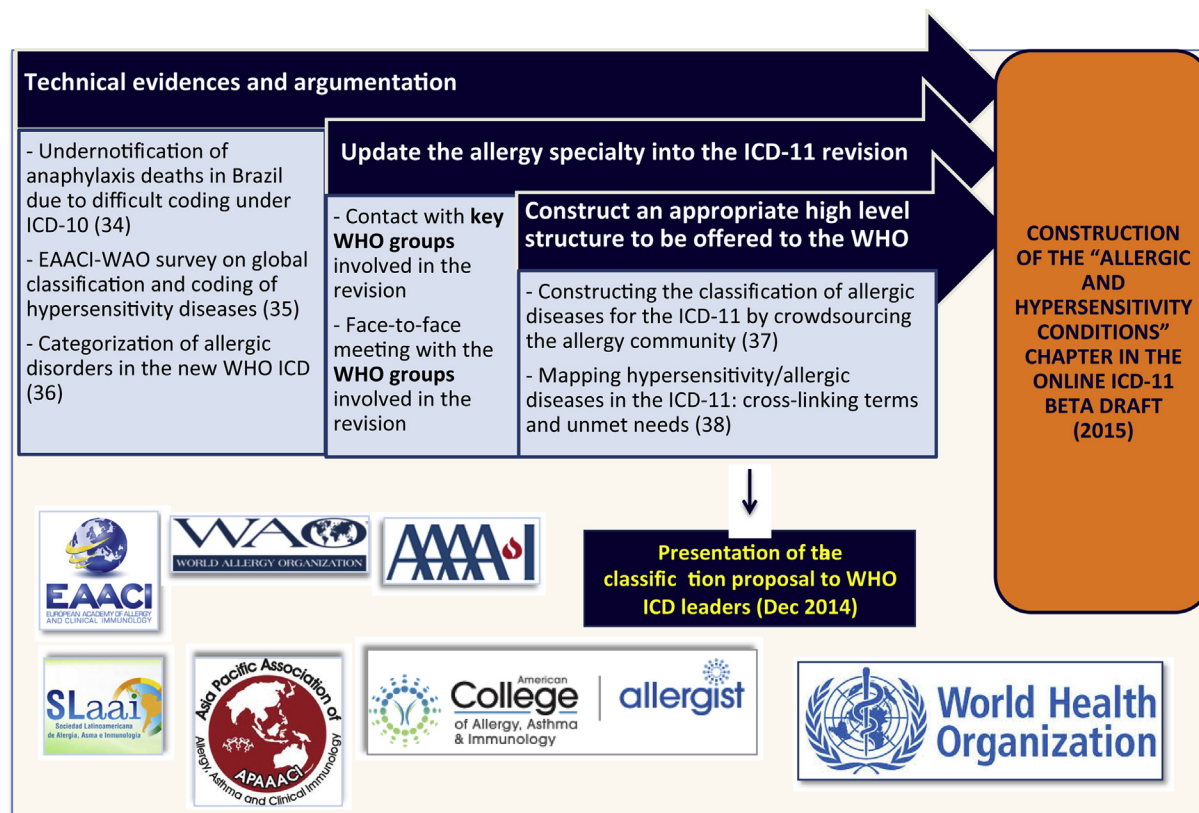
The 11th revision of the ICD was initiated by the Director of the Department of Health Statistics and Information Systems at the WHO in 2011 and intends to be presented to the World Health Assembly in 2017. The current infrastructure of the ICD-11 has 27 chapters updated regularly by collaborative web-based editing and follows the WHO concern on being delineated by a scientific basis to ensure comparability and consistency and to allow flexibility of the tool to fit different purposes.

Some countries will create a national modification of the ICD for their own use and these will contain more specific information or details than can be found in the WHO ICD (eg, Australia has ICD-10-AM, Canada has ICD-CA, and the USA has ICD-10-CM). All updates to the main ICD are done through the WHO. Once the ICD-11 is available, all the countries currently using the national modifications will be advised to move to the ICD-11.

Constructing a classification of allergy and/or hypersensitivity conditions for the ICD-11

In 2012, we proved that the ICD-10 is not able to provide reliable anaphylaxis deaths data due to the difficulty of coding, resulting in the undernotification of this condition.³⁶ However, the misclassification did not concern just anaphylaxis, but all allergy and/or hypersensitivity conditions.

Understanding that the 11th revision of the ICD offers a unique opportunity to improve the classification and coding of allergy and/or hypersensitivity conditions, an international collaboration of Allergy Academies, first including the European Academy of Allergy and Clinical Immunology, World Allergy Organization, and American Academy of Allergy Asthma and Immunology and then the Latin American Society of Allergy,



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FIGURE 1. Strategic action plan to update allergic and hypersensitivity conditions in the International Classification of Diseases (ICD)-11.

Asthma and Immunology; the Asia Pacific Association of Allergy, Asthma and Clinical Immunology; Asia Pacific Association of Pediatric Allergy, Respiratory and Immunology; and the American College of Allergy, Asthma and Immunology, has been supporting strategic actions to strengthen our specialty by the inclusion of a specific dedicated chapter. Since 2013, we have spent tremendous efforts to have a better classification of these disorders in the forthcoming ICD-11 version (Figure 1). The strategic action plan was based on (i) providing scientific and technical evidence for the need of changes, (ii) update the allergy specialty in the ICD-11 revision, and (iii) construct an appropriate high-level structure to be offered to the WHO. All the actions so far have been supported and acknowledged by the main allergy academies and we have been documenting all the steps by publications.³⁶⁻⁴⁰ As a result, we have been working together with the WHO representatives, and a chapter addressed to allergic diseases was constructed into the ICD-11. We are proud to announce the construction of the "Allergy and Hypersensitivity conditions" parent chapter in the ICD-11, ready for field trials and final approval by the World Health Assembly in 2017.

Exploring allergy and/or hypersensitivity diagnostic procedures in the ICD-10 and ICD-11 frameworks

Constructing a classification of allergy and/or hypersensitivity conditions for ICD-11 was a challenge, but it exclusively creates appropriate codes for our diseases of interest, assuming that the final diagnosis is correct. It should however be linked to our *in vitro* and *in vivo* diagnostic procedures. The diagnostic

procedures codification changes into the ICD will clearly impact our specialty. We therefore decided in this article to review them so as to have a baseline and to elicit suggested changes and/or new proposals.

In the first phase of this project, we were able to prepare a list of the important allergy and/or hypersensitivity diagnostic procedures (key words) that health care professionals are using on a daily basis (Table I). We are aware that some biological *in vitro* tests are in use just in the research settings of some centers in some countries, but we acknowledged their significance because of the increasing number of related publications. The main published guidelines in this field¹⁻³⁴ were the basis of the construction of the proposed categories list, which was first validated independently by the first and last authors to avoid missing terms and then reviewed by the co-authors. The outcome of this academic process was a list of 17 key words that we distributed in 2 main domains, (a) "*in vivo* tests for the diagnosis of allergy and hypersensitivity conditions" and (b) "*in vitro* tests for the diagnosis of allergy and hypersensitivity conditions," under the heading "special screening examination and diagnosis for allergy and hypersensitivity conditions." We limited this core list of allergy and/or hypersensitivity diagnostic procedures based on (I) frequency of use by allergists worldwide; (II) specificity of diagnostic methods, excluding for example total serum IgE measure; (III) methods not covered by other specialties; and (IV) methods already mentioned in the ICD framework. We also considered the fact that the network of WHO Collaborating Centers for Family of International Classifications has promoted the development of the International

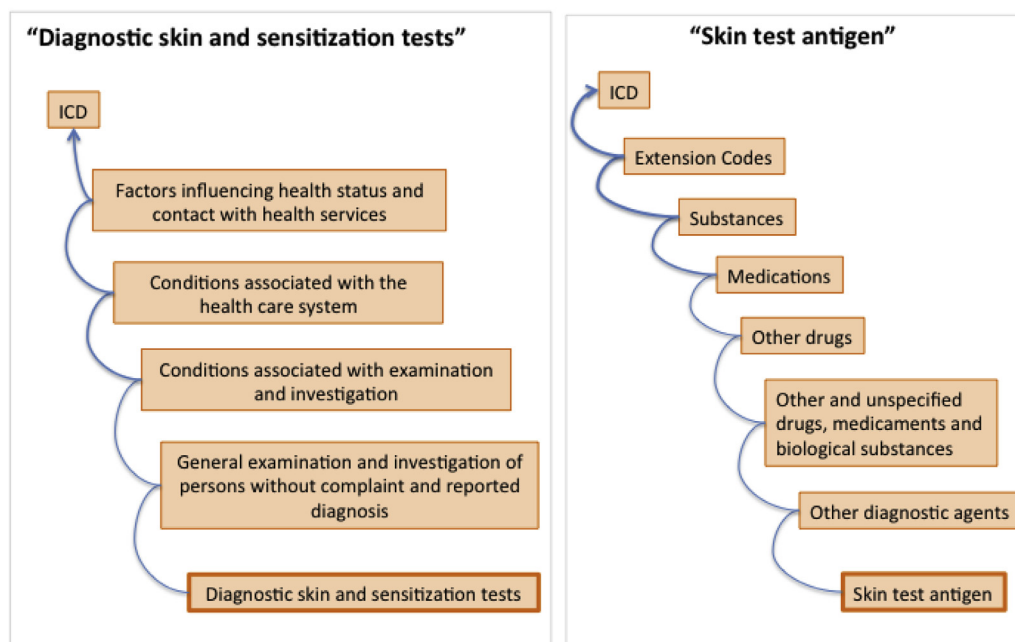
ICD-11 Foundation Hierarchies
(June 2015 version)

FIGURE 2. Hierarchies of allergy diagnostic procedures in the current International Classification of Diseases (ICD)-11 foundation (June 2015 version).

TABLE II. Search terms process of the main diagnostic procedures for allergy and/or hypersensitivity

Terms searched	ICD-10 (2015 version, access June 2015)	ICD-11 Foundation (June 2015 version)
"Skin test"	R76.1 "Abnormal reaction to tuberculin test" Z01.5 "Diagnostic skin and sensitization tests" X44 "Accidental poisoning by and exposure to other and unspecified drugs, medicaments, and biological substances" Y14 "Poisoning by and exposure to other and unspecified drugs, medicaments, and biological substances, undetermined intent" X64 "Intentional self-poisoning by and exposure to other and unspecified drugs, medicaments, and biological substances"	"Photoallergic allergic reaction" "Diagnostic skin and sensitization tests" "Lygranum (skin test)" "Mumps skin test antigen" "Skin test antigen" "Acromegaly and pituitary gigantism" "Latent late syphilis" "Cockayne syndrome" "Mixed connective tissue disease" "Major hypertriglyceridemia" "Netherton syndrome" "Encephalopathy due to sulfite oxidase deficiency"
"Provocation test" or "Challenge test"	Search did not find any results	Search did not find any results
"Specific IgE" or "Allergen-specific IgE"	Search did not find any results	Search did not find any results
"Tryptase"	Search did not find any results	"Anaphylaxis secondary to mast cell disorder"

Corresponding ICD-10 codes highlighted in bold.

Classification of Health Interventions. It is currently under adaptation to meet present day conformance criteria with recognized standards and follow a rapid change in science and technology. It is intended to be used in countries that do not, as yet, have their own classification of interventions.

In the second phase, all possible and relevant corresponding terms were selected from the ICD-10⁴¹ and the ICD-11 β phase foundation.⁴² We used an online process to search the key words corresponding to both ICD-10 (2015 version) and ICD-11

β draft (June 2015 version). We observed that more than 90% of very specific and important diagnostic procedures in use by the allergists' community on a daily basis are missing (Table II), including skin prick tests or skin patch tests. For those terms, the initial search process was unsuccessful; we decided for more general terms (eg, "skin tests" instead of "skin prick tests" or "intradermal skin test" and "tryptase" for "serum tryptase"). To refine the search process, we tried to use some similar terms such as "challenge test" for "provocation test."

TABLE III. Special screening examination and diagnostic procedures for allergy and hypersensitivity conditions in the ICD-11

Special screening examination and diagnosis for allergy and hypersensitivity conditions	Definition of procedures used in the allergy and hypersensitivity conditions investigation
<i>In vivo</i> tests for the diagnosis of allergy and hypersensitivity conditions	
1. Skin allergen tests	Skin tests are used to prove sensitization, meaning the presence of specific IgE or T lymphocyte to an allergen. It proves underlying immune mechanism, but the results of these procedures have to be associated with a specific compatible clinical history to lead to the diagnosis of allergy. Skin tests to prove sensitization are not usually indicated as a screening of the general population and have to receive a careful interpretation.
1.1 Skin allergen prick test	Skin prick tests (SPT) demonstrate a sensitization response to a specific allergen. In conjunction with an allergy-focused history, SPT help to confirm the presence of an allergy to a food, drug, or inhaled substance (allergen). This <i>in vivo</i> cutaneous method is widely used to demonstrate an immediate IgE-mediated allergic reaction.
1.2 Intradermal allergen test	The intradermal test is an <i>in vivo</i> method in which a tiny quantity of allergen is injected in the dermis with a hypodermic needle. It is indicated for the diagnosis of both IgE and T-lymphocyte-mediated allergic conditions.
1.3 Skin patch test	Skin patch test (PT) is the gold standard <i>in vivo</i> test procedure to confirm T-lymphocyte-mediated allergic diseases and/or sensitization in subjects with allergic contact dermatitis, atopic eczema, as well as some food and drug allergies. It provides evidence of sensitization and can confirm the etiological diagnosis of a suspected T-lymphocyte-mediated (type IV) allergy by reproducing a local allergic reaction on a small area, where the diluted test substances are placed.
1.3.1 Skin photopatch test	Photopatch testing is used to establish a diagnosis in patients with suspected photodermatoses and to determine threshold dose and wavelength dependence. PT with the potential photosensitizer is simply UV irradiated.
2. Provocation test <i>Incl.</i> : Challenge test	The provocation test is the gold standard <i>in vivo</i> diagnostic procedure in which there is a controlled administration a substance, suspected to be the allergy and/or hypersensitivity conditions causal agent and/or trigger. During the test, the patient is exposed to a given allergen source in a safe place, under a standardized protocol. It is used to confirm the diagnosis, to provide a safe alternative, to follow up previous diagnosis of allergy and as a pharmacological model to test new compounds to treat allergic symptoms. It is very important that they be indicated, supervised, and interpreted by an allergist.
2.1 Conjunctival allergen provocation test	The conjunctival allergen provocation test involves the instillation of defined concentrations of an allergen solution on the conjunctiva to elicit an IgE-mediated allergic reaction of the ocular surface mucosa, in a presumed sensitized patient.
2.2 Food allergen provocation test	The food allergen provocation test provides a gold standard diagnostic for food-related adverse reactions leading to appropriate food avoidance. The test is also indicated for follow-up of previously diagnosed food sensitivities. During the test, the patient is exposed to a given food in a safe place, under a standardized protocol.
2.3 Drug provocation test	A drug provocation test is the controlled administration of a drug to diagnose drug allergy and/or hypersensitivity reactions. These procedures are performed under medical surveillance, whether this drug is an alternative compound, or structurally and/or pharmacologically related, or the suspected drug itself.
2.4 Bronchial allergen provocation test	Bronchial allergen provocation test is the bronchial exposure of controlled progressive doses of a specific allergen. This <i>in vivo</i> test is used to confirm the diagnosis when there are discrepancies between history and results of SPT or specific IgE measurement, to confirm the diagnosis of occupational asthma, to demonstrate late airway response, and to confirm the diagnosis in a patient who has difficulty accepting the consequences of disease. It is also used as pharmacological model to test new compounds to treat allergic asthma.

(continued)

TABLE III. (Continued)

Special screening examination and diagnosis for allergy and hypersensitivity conditions	Definition of procedures used in the allergy and hypersensitivity conditions investigation
2.5 Nasal allergen provocation test	Nasal allergen provocation test is the nasal exposure of controlled progressive doses of a specific allergen. This <i>in vivo</i> method used to confirm the burden of allergen-induced symptoms and select an allergen in polysensitized patients, to confirm the diagnosis when there are discrepancies between history and results of SPT or specific IgE measurement, to confirm the diagnosis of occupational allergic rhinitis or local allergic rhinitis, and to confirm a diagnosis in a patient who has difficulty accepting the consequences of disease. It is also used as pharmacological model to test new compounds to treat allergic rhinitis.
Other <i>in vivo</i> tests for the diagnosis of allergy and hypersensitivity conditions	
<i>In vitro</i> tests for the diagnosis of allergy and hypersensitivity conditions	<i>In vitro</i> assays have been developed to augment the allergy clinical history and skin test results.
1. Serum allergen-specific IgE	An allergen-specific immunoglobulin E (IgE) quantification blood test is performed to check whether a person is sensitized to a particular substance previously exposed. In conjunction with an allergy focused history and often SPT, it is used to ascertain a suspected IgE-mediated reaction.
2. Basophil activation test	Basophil activation test (BAT) is an <i>in vitro</i> method indicated to quantify the expression of activation markers (eg, CD63) on basophil surface, preferably in whole blood, by flow cytometry on allergen stimulation. It is viewed as a multifaceted and promising tool for the allergists in cases of IgE-mediated reactions.
3. Serum tryptase	Serum (or plasma) tryptase is an <i>in vitro</i> method used during the acute phase of a reaction that reflects the mast cell degranulation. Elevated levels of tryptase occur in cases of anaphylaxis (immune or nonimmune mediated) and in systemic mastocytosis. Total tryptase levels generally reflect the increased burden of mast cells in patients with all forms of systemic mastocytosis and the decreased burden of mast cells associated with cytoreductive therapies in these disorders.
4. Lymphocyte transformation (blood) test	The lymphocyte transformation test (LTT) is an <i>in vitro</i> test, which measures the proliferation of T cells to a hapten. It proves that the hapten tested is responsible for the reaction in subjects previously sensitized to this substance. This concept of the LTT has been confirmed by the generation of hapten-specific T-cell clones.
Other <i>in vitro</i> tests for the diagnosis of allergy and hypersensitivity conditions	

The search for “skin tests” in both the ICD-10 and ICD-11 foundation resulted in many different terms, most of them not related to allergy, but we noticed the entries “diagnostic skin and sensitization test” in both ICDs and “skin test antigen” in the ICD-11. However, when we looked for the hierarchies in the ICD-11 foundation (June 2015 version) of these 2 entries, we observed that they are not appropriately placed (Figure 2). For “diagnostic skin and sensitization test,” it is scattered under the “General examination and investigation of persons without complaint and reported diagnosis,” meaning that some concepts usually used by the allergist community on a daily basis are not fully recognized by other specialties, such as the definitions of “sensitization” and “allergy.” The scenario is similar for “skin test antigen,” which is listed in the Extension codes chapter, but under “Other and unspecified drugs, medicaments and biological substances.” Besides skin tests, no other typically used allergy procedures had been considered in the ICD-10 and current ICD-11 structures.

The whole scheme and the correspondence in ICD-10 (2015 version) and ICD-11 foundation (June 2015 version) provided us a big picture of the missing or imprecise terms and how they

are scattered in the current ICD-11 framework, allowing us to submit new proposals to increase the visibility of the allergy and/or hypersensitivity diagnostic procedures (Table III) as well as to contribute in the updates of the International Classification of Health Interventions.

Implementation of allergy and/or hypersensitivity diagnostic procedures in the ICD-11

With the aim of actively supporting changes in favor of our specialty, we intended to use the results of the current manuscript to base new proposals to be submitted into the ICD-11 platform.⁴² For that, we worked in 2 main actions. The first was building a structure with all key words and definitions able to fit the ICD content model (Table III). Each of the key words was submitted into the ICD-11 β draft platform following the WHO guidance and substantiated by contemporary guidelines in the field.

The second action was based on the hierarchies of the entries already listed in the ICD-11 framework. The proposals of tuning the titles and the position in which they were listed were substantiated by the current definitions in use by the allergy

community worldwide. The misunderstanding of our concepts and definitions supports the need of a strategic plan of dissemination.

Currently, we are unable to objectively measure the consequences of these changes in the ICD framework, but we strongly believe that the outcomes of all past and future actions will impact positively as an aggregate data to perform positive quality improvement in health professional clinical practice. As an example, in many countries, both public and private health systems operate using the ICD for the reimbursement of procedures. Therefore, the absence of a well-defined procedure in this international system may have direct economic impact.

In conclusion, the forthcoming ICD-11 with the changes we proposed will allow providers to better track allergy and/or hypersensitivity patient care and aggregate data to perform quality-improvement analysis. We believe that our actions will increase the visibility of the allergy and/or immunology specialty and the conditions we treat and study.

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