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International consensus criteria for the diagnosis of Raynaud's phenomenon

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ABSTRACT

Vasoconstriction accompanied by changes in skin color is a normal physiologic response to cold. The distinction between this normal physiology and Raynaud's phenomenon (RP) has yet to be well characterized. In anticipation of the 9th International Congress on Autoimmunity, a panel of 12 RP experts from 9 different institutes and four different countries were assembled for a Delphi exercise to establish new diagnostic criteria for RP. Relevant investigators with highly cited manuscripts in Raynaud's-related research were identified using the Web of Science and invited to participate. Surveys at each stage were administered to participants via the on-line SurveyMonkey software tool. The participants evaluated the level of appropriateness of statements using a scale of 1 (extremely inappropriate) through 9 (extremely appropriate). In the second stage, panel participants were asked to rank rewritten items from the first round that were scored as "uncertain" for the diagnosis of RP, items with significant disagreement (Disagreement Index > 1), and new items suggested by the panel. Results were analyzed using the Interpercentile Range Adjusted for Symmetry (IPRAS) method. A 3-Step Approach to diagnose RP was then developed using items the panelists "agreed" were "appropriate" diagnostic criteria. In the final stage, the panel was presented with the newly developed diagnostic criteria and asked to rate them against previous models. Following the first two iterations of the Delphi exercise, the panel of 12 experts agreed that 36 of the items were "appropriate", 12 items had "uncertain" appropriateness, and 13 items were "inappropriate" to use in the diagnostic criteria of RP. Using an expert committee, we developed a 3-Step Approach for the diagnosis of RP and 5 additional criteria for the diagnosis of primary RP. The committee came to an agreement that the proposed criteria were "appropriate and accurate" for use by physicians to diagnose patients with RP.

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1. Introduction

Raynaud's phenomenon (RP), named after the French physician Maurice Raynaud (1834–1881), is a disorder of the microvasculature that generally affects the fingers and toes but can present on

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other extremities such as the nose, ears and nipples [1–3]. Raynaud first characterized the disease in his 1862 thesis, believing his patients' symptoms resulted from deregulated constriction of precapillary arterioles caused by an overactive neurological reflex [4]. Clinically, Raynaud's is often sub-classified into primary RP, which runs a relatively benign course, and secondary RP, which is either associated with or predates an underlying systemic connective tissue disease [3–6]. Primary RP is generally symmetric in presentation, lacks any evidence of necrosis, and patients are seronegative for ANA, whereas patients with secondary RP may suffer from digital pitting, ulceration and even dry gangrene [3,7]. Regardless of the subtype, the hallmark of RP is ischemia of the digits in response to cold, which produces a characteristic "triphasic" color pattern, (pallor, cyanosis, rubor) as well as numbness and swelling [2,8]. Initially, the distal finger pads become pale, or turn white due to constricted blood-flow; then become blue, a sign of tissue hypoxia; and lastly red, as the tissue is reperfused [3,9]. Well-demarcated color changes are considered by some to be an important diagnostic hallmark of RP, but without direct observation of an attack, it may be difficult to assess this feature [2,8]. RP is fairly common, affecting 3–5% of the global population with a shift in prevalence toward colder climates [2–4].

The most common trigger is thought to be exposure to cold. Attacks may even occur after minor changes in temperature, such as moving into an air-conditioned building from a hot summer day [3,10]. Other reported triggers include emotional stress; medications such as beta-blockers; injury due to vibrations or forcible trauma; extended use of digits, as with prolonged periods of typing; smoking; and the presence of other arterial diseases, such as vasculitis [11].

In 10–20% of cases, RP is the initial manifestation of an associated underlying connective tissue disease, such as scleroderma, dermatomyositis, systemic lupus erythematosus, mixed connective tissue disease, Sjögren's syndrome, and rheumatoid arthritis [3].

Despite the widespread prevalence of RP, standardized diagnostic criteria have not been thoroughly established. Brennan et al., Wigley, LeRoy and Medsger, and Maricq et al. have all developed and published diagnostic criteria for RP (Table 1), but the use of these criteria has been limited in the clinical setting [4,7,12,13]. Herein we report the results of a Delphi exercise in which an international panel of experts came to an "agreement" on new diagnostic criteria for RP, which was then validated mathematically using the IPRAS method.

2. Methods

A Web of Knowledge search for highly cited authors identified 14 physicians from 4 countries and 9 universities as experts in both RP and connective tissue diseases. The 14 experts were then emailed invitations to participate in the Delphi consensus-building exercise. One physician failed to respond to the invitation, one physician declined, and the remaining 12 agreed to participate (Fig. 1). The participating committee members were sent the first round online-survey consisting of 49 statements/items regarding the diagnosis of RP. The names of the panelists were kept confidential and all responses were de-identified prior to releasing them to the group [14]. This allowed each member to answer questions without being influenced by the opinions of the other panelists.

The criteria presented for committee scrutiny were assembled from Pubmed literature searches and highly-cited manuscripts on RP identified by the Web of Science. Additionally, previously established RP diagnostic criteria were used to formulate statements presented to the panel [1–4,8,12,13,15–29]. The panel was asked to rate each item using a 9-point scale according to how discriminatory they felt each was in successfully identifying patients with RP. A rating of 1 was defined as being "extremely inappropriate" and a rating of 9 was defined as "extremely appropriate". The RP experts were asked not to consider cost or feasibility of implication when providing their ratings for each item.

Table 1
Prior diagnostic criteria for Raynaud's phenomenon (RP).

Classification criteria based on clinician's assessment	Ask the following screening questions	Criteria for the diagnosis of primary Raynaud's phenomenon	Classification scheme based on color charts and questionnaire
Negative: Absence of episodes of color change (pallor, cyanosis, erythema), or symptoms (paresthesia, numbness) on exposure to cold *Possible*: Episodes of uniphasic change (one of pallor, cyanosis, erythema), and/or paresthesia or numbness. *Definite*: Repetitive episodes of biphasic color (at least two or pallor, cyanosis, erythema), in either cold or normal environments. *Severe*: Repetitive episodes of biphasic color (at least two of pallor, cyanosis, erythema), in addition to paresthesia or numbness, occurring in both cold and normal environments.	1.Are your fingers unusually sensitive to cold? 2.Do your fingers change color when they are exposed to cold temperatures? 3.Do they turn white, blue, or both? The diagnosis of Raynaud's phenomenon is confirmed by a positive response to all three questions. If positive for diagnosis of Raynaud's phenomenon, further criteria for the distinction of Primary versus Secondary RP are then evaluated for.	- Vasospastic attacks precipitated by cold or emotional stress - Symmetric attacks involving both hands - Absence of tissue necrosis or gangrene - No history or physical findings suggestive of a secondary cause - Normal nail-fold capillaries - Normal erythrocyte sedimentation rate - Negative serologic findings, particularly negative test for antinuclear antibodies	*Questionnaire*: a. Are your fingers sensitive to cold? b. Do your fingers show unusual color changes, and if 'Yes,' do they become white, blue, red, or purple? *Negative*: No blanching by hand photograph or color scale *Possible*: Blanching by hand photograph and/or color scale but insufficient for definite *Definite*: At least three of the following: 1. Blanching by hand photograph 2. Blanching by color scale 3. Yes to question (a) 4. Yes to question (b)
Source: Brennan et al.[a]	Source: Wigley[b]	Source: LeRoy et al.[c]	Source: Maricq et al.[d]

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