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# Applying the phenotype approach for rosacea to practice and research\*

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## Summary

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**Background** Rosacea diagnosis and classification have evolved since the 2002 National Rosacea Society expert panel subtype approach. Several working groups are now aligned to a more patient-centric phenotype approach, based on an individual's presenting signs and symptoms. However, subtyping is still commonplace across the field and an integrated strategy is required to ensure widespread progression to the phenotype approach.

**Objectives** To provide practical recommendations that facilitate adoption of a phenotype approach across the rosacea field.

**Methods** A review of the literature and consolidation of rosacea expert experience.

**Results** We identify challenges to implementing a phenotype approach in rosacea and offer practical recommendations to overcome them across clinical practice, interventional research, epidemiological research and basic science.

**Conclusions** These practical recommendations are intended to indicate the next steps in the progression from subtyping to a phenotype approach in rosacea, with the goals of improving our understanding of the disease, facilitating treatment developments and ultimately improving care for patients with rosacea.

### What's already known about this topic?

- Rosacea diagnosis and classification have evolved from a subtype to a phenotype approach.
- Adoption of the phenotype approach has begun, but more widespread adoption and support across the field are required to ensure a complete transition.

### What does this study add?

- We offer practical guidance for clinical practice, interventional and epidemiological research, and basic science, to help overcome challenges and facilitate comprehensive uptake of the phenotype approach in rosacea

Rosacea diagnosis and classification have evolved. In 2002, the National Rosacea Society (NRS) expert panel proposed diagnostic criteria for rosacea and an associated subtype-based classification that grouped the most common presentations according to disease features.<sup>1</sup> These diagnostic criteria and the subtype classification have guided the majority of subsequent publications on rosacea diagnosis and treatment.<sup>2–8</sup>

However, progress in rosacea research over the last decade has revealed important limitations of this approach.<sup>9</sup> As a consequence, three working groups [the American Acne and Rosacea Society (AARS), the global rosacea consensus expert panel (ROSCO) and the NRS] have formalized what many dermatologists already do in clinical practice and updated the methodology for diagnosis based on phenotypes of the disease.<sup>9–14</sup>

The recommendations for a phenotype approach to rosacea, where the disease is diagnosed and classified according to an individual's presenting features instead of those grouped by subtypes, acknowledge the limitations of subtyping, and build on previous recommendations to propose an approach based on an individual patient's presenting signs and symptoms. Table 1 shows a comparison of rosacea according to the NRS 2002 subtype classification and the aligned 2017 ROSCO and revised 2017 NRS phenotype recommendations. The features listed under the 2017 system can be combined into any presentation, provided the diagnostic criteria are met. Conversely, the previous 2002 subtype system combined multiple features into the erythematotelangiectatic, papulopustular, phymatous and ocular subtypes.<sup>1,11,13</sup>

Elements of a phenotype approach have been incorporated into recent national treatment recommendations, which advocate targeted treatment of individual rosacea features.<sup>15–18</sup> However, subtyping is still commonplace in numerous recent publications.<sup>19,20</sup> In order to promote wider implementation of a phenotype approach, it is important first to identify

challenges preventing this transition and then to develop strategies to address those challenges.<sup>21</sup>

Common challenges to implementation include: poor support and organizational structures within the healthcare system; insufficient knowledge, awareness or skill; lack of resources including time; and uncertainty over the legitimacy of new recommendations.<sup>22</sup> In the present publication, we identify challenges to implementation of a phenotype approach across clinical practice, interventional research, epidemiological research and basic science in rosacea. We then make practical recommendations to facilitate assessment, management and research progression inclusive of the individual experience of disease.

## Materials and methods

A panel of four dermatologists defined the framework for possible recommendation categories pertaining to clinical practice, interventional research, epidemiological research and basic science in rosacea. A literature search was performed to assess the current approach to rosacea practice and research within these four areas. Hits were limited to articles published between April 2015 and January 2018 to cover the period after publication of the most recent Cochrane systematic review on interventions for rosacea.<sup>19</sup> The authors identified challenges to implementation of a phenotype approach based on the literature search results and their experience in the field. They then consolidated and refined their recommendations through discussion.

## Challenges

Fifteen years' usage of the NRS 2002 rosacea diagnostic criteria and subtyping in textbooks, academic papers and podium presentations has engrained these concepts in dermatology. There is a need for clinicians, researchers, authors and scientific reviewers to be apprised of current modifications. Until then, the subtype concept with its shortcomings will persist.

Inconsistent nomenclature is a field-wide issue that confounds the reporting of numerous studies. The terms 'rosacea' and 'acne rosacea' are used variably and often nonspecifically, as are definitions of certain features (e.g. persistent and transient erythema can be confounded with perilesional inflammation). There is a need for better differentiation in research studies of the phenotype of the patients being studied.

The challenges in interventional research mostly centre on existing conventions and protocols. As the transition towards a phenotype approach is a recent development, little documentation exists to demonstrate its benefits and convince stakeholders of its value. In addition, older treatments assessed according to subtype in previous literature (e.g. Cochrane systematic reviews) will be disqualified, while new, smaller studies may be required to show an effect of a therapy, either alone or in combination, on specific features.

Industry sponsors of interventional research using subtype-based measures may be reluctant to replace these with outcomes for individual features, unless the value has already

**Table 1** Summary of recommendations for rosacea diagnosis, according to the 2002 subtype and 2017 phenotype approaches

NRS 2002 <sup>1</sup>	
Primary (diagnostic) features <sup>a</sup>	Flushing/transient erythema Nontransient/persistent erythema Papules and pustules Telangiectasia
Secondary features	Burning/stinging sensation Oedema Dry appearance Ocular manifestations Plaque
ROSCO 2017/NRS 2017 <sup>11,13</sup>	
Diagnostic features <sup>b</sup>	Persistent centrofacial erythema with periodic intensification by potential trigger factors Phymatous changes
Major features <sup>c</sup>	Transient centrofacial erythema Inflammatory papules/pustules Telangiectasia Ocular manifestations
Minor/secondary features	Burning/stinging sensation Oedema Dry sensation/appearance
According to the 2002 subtyping system, multiple features were grouped into defined subtypes. The 2017 phenotyping system allows various combinations of diagnostic, major and minor features into an individual phenotype. NRS, National Rosacea Society; ROSCO, global ROSacea Consensus panel. <sup>a</sup> The presence of one or more of these with a central facial distribution is indicative of rosacea. <sup>b</sup> Individually diagnostic. <sup>c</sup> A combination of at least two is diagnostic, in the absence of a diagnostic feature. Individual publications also discuss the importance of proper history taking, exclusion criteria and trigger factors for specific features.	

been demonstrated. We believe that the phenotype approach allows investigators to assign outcomes for one or more rosacea features best addressed by investigational treatments, compared with multiple features in some existing scales. Standardizing these outcome measures would also facilitate interstudy comparisons and combining of results. Furthermore, improved severity scales that focus on individual features should be more accurate than those in current usage, thereby offering the potential for a smaller trial population to demonstrate significance. This could translate to lower costs of trials.

Study protocols are a further challenge for adoption of a phenotype approach in interventional and epidemiological research, due to the engrained subtype-based nomenclature. Some researchers accept implicitly that a singular examination predicates the features of an individual patient with rosacea; this fails to account for fluctuation of some features over time (e.g. papules/pustules or erythema with phyma) and may provide an incomplete disease representation for the patient. This is also hindered by the lack of long-term epidemiological studies in the field. Furthermore, darker skin pigment phototypes are under-represented in epidemiological studies, due to difficulties in diagnosis that often fail to account for the presence of rosacea in these patients.

In basic science, several specific factors also hinder the progression to a phenotype approach to rosacea. These include limited funding opportunities, absence of patient registries or clinical tissue biobanks, and the lack of a satisfactory animal model for rosacea.

## Results

### Challenges and recommendations for clinical practice

A phenotype approach to rosacea management could improve patient outcomes by targeting the aspects most bothersome to the patient.<sup>12</sup> It also facilitates use of combination therapy when necessary, to address multiple presenting features and optimize clinical outcomes and quality of life.<sup>12</sup> Rosacea treatment is moving towards such an approach, which is now recommended by several regional and national bodies in clinical practice.<sup>15–18</sup> However, further support is needed to facilitate its implementation into daily practice.

Assessment of disease severity and patient impact (including quality of life) would also benefit from a phenotype approach. Several groups have commented that existing scales for assessing these are not sufficient, including the only rosacea-specific tool (Rosacea Quality of Life; RosaQoL), which both omits certain features and lacks indication of a clinically relevant difference. As such, there is a need for validated tools that are easy to use in the clinic and address all skin pigment types.<sup>9,11,13,23</sup>

### Recommendations

1. Update the language surrounding rosacea diagnosis and classification to discontinue the concept of subtyping.

- Includes updated phraseology in textbook revisions, as well as forthcoming publications.
- 2. Initiate an international, multisponsor core meeting of stakeholders to develop a communications plan for the phenotype concept.
  - Supported by specific sessions at the societies' associated international congresses to bring the rosacea phenotyping concept to the forefront, with subsequent sessions at national meetings.
- 3. Educate patients and healthcare providers to raise awareness and improve understanding of the phenotype nomenclature.
  - Education should be targeted to specific groups, including patient support organizations, dermatologists and general practitioners.
  - Requires promotion to multiple national and international organizations for patients with skin disease.
- 4. Demonstrate the proven clinical value of making the change to phenotyping and reinforce the shortcomings of the subtype approach.
  - Also requires studies that demonstrate the effect of different drugs, individually and in combination, on specific rosacea features, together with appropriate communication of the results.
- 5. Develop simple clinical tools for physicians to use with their patients that are applicable to all skin pigment types.
  - Should include clear definitions of individual rosacea features and their specific burden, to aid the physician in treating the features most bothersome to the patient.
  - Should align with treatment goals, with clear skin being a key objective.
  - See Appendix S1 in the Supporting Information for a downloadable checklist to document clinical signs and symptoms (i.e. the patient's specific phenotype) and correlate this with therapeutic approaches.

### Challenges and recommendations for interventional research

Assessment methodologies used in rosacea clinical trials are variable and could be of higher quality.<sup>19,23</sup> The subtype approach is likely to hinder treatment progress in two ways. Firstly, a treatment directed at one dimension of a subtype (e.g. inflammatory papules or pustules in papulopustular rosacea) may fail in clinical trials because it does not address the subtype's other dimensions (i.e. persistent erythema).<sup>11</sup> Secondly, the multiple dimensions of a subtype can confound commonly used rosacea severity scales, as with clinical practice. In clinical trials, this can interfere with study and assessment of the course of singular disease features.<sup>9</sup>

Many clinical trials in rosacea still recruit patients using subtype-based inclusion criteria and assess treatment outcomes according to those subtypes (for example, using the NRS Rosacea Clinical Scorecard).<sup>19</sup> However, although some more recent studies have still recruited patients by subtype, they have assessed therapeutic response by change in individual features.<sup>24–27</sup> This is a positive step towards a phenotype approach.

### Recommendations

1. Establish credible, standardized clinical and patient-reported measures for the most common features to make them acceptable to researchers, industry and regulatory authorities.
  - Industry may be especially interested in moving forward new drug entities to address specific signs and symptoms instead of the multiple dimensions required with subtypes.
2. Develop and publish real-life examples of phenotype use in interventional research, to validate the approach and demonstrate best practice throughout the field.
  - Could be based on the five-part AARS series, suggesting that a phenotype evaluation of rosacea correlates with therapy.<sup>10,28–31</sup>
  - Enhance with the support of a larger group of interested researchers and clinicians.

### Challenges and recommendations for epidemiological research

Epidemiological studies in rosacea provide widely varying disease prevalence estimates. Beyond valid differences relating to location and population differences, this variation may be a result of differences in case determination and study design, and variable assessment of individual features due to differences in skin pigment type.<sup>14</sup>

Characterizing by subtype confounds epidemiological studies because many patients present with varied features, so are inadequately described. For example, there is no subtype for a patient presenting solely with persistent centrofacial erythema without transient erythema and flushing, or vice versa. Similarly, a patient presenting with fixed erythema, inflammatory papules and pustules and telangiectasia could fall into both the erythematotelangiectatic and papulopustular categories, and so might be counted twice.<sup>9</sup> Furthermore, certain features can spontaneously remit and recur, which may result in the patient being classified in multiple subtype categories dependent on the time of observation.<sup>32</sup>

Refining diagnostic criteria based on a phenotype approach could improve the consistency and quality of epidemiological data, which would continue to benefit rosacea diagnosis and overall disease management.<sup>14</sup>

### Recommendations

1. Facilitate longitudinal epidemiological studies in rosacea that consider the potential for fluctuation of certain features.
  - There would be great value in extension to a global registry, which would provide longitudinal real-world evidence to bolster epidemiological data and a phenotype treatment approach.
2. Include and support regional groups from all continents in epidemiological studies, to ensure representation of all skin pigment types.

### Challenges and recommendations for basic science

Despite ongoing research, the pathophysiology of rosacea remains uncertain. Cutaneous rosacea subtypes demonstrate both differences and overlap in histological, immunohistological and gene expression markers. As such, there is limited information on molecular markers responsible for the initiation and perpetuation of rosacea's various cutaneous features.<sup>9,33–35</sup> Therefore, subtype classification may be hindering biomarker identification for individual features.

### Recommendations

1. Work towards highlighting the need for national initiatives to support research in rosacea.
  - For example, the National Institutes for Health Request for Applications.
2. Extend clinical practice updates that emphasize phenotype nomenclature to basic science.
  - Would be of similar benefit in standardizing assessments.
3. Reinforce the concept of phenotype variation over time, as with epidemiological research.
  - Would encourage specimen collections at multiple time points to assess the chronic nature of the disease.
4. Interrogate existing data to unmask key specific factors in rosacea pathophysiology and identify which treatments have the largest or fastest impact on disease.

### Discussion

Herein we have discussed strategies to support the phenotype approach in rosacea across clinical practice, interventional and epidemiological research, and basic science. Several strategies span multiple areas, which reflects the need for an integrated approach to ensure consistent and comprehensive uptake.

**Table 2** Key strategies for implementing change from the Expert Recommendations for Implementing Change and their context in rosacea

Key activities for strategy implementation <sup>39</sup>	Relevance to rosacea and current status	
	Underway	Future work
<b>Build a coalition:</b> recruit and cultivate relationships with partners in the implementation effort	Global, regional and national working groups are becoming aligned to adoption of a phenotype approach	Instigate a core meeting at international congresses via partnerships with international or regional societies, with cascades down to national meetings
<b>Develop an implementation glossary:</b> develop and distribute a list of terms describing the innovation, implementation and stakeholders in the organizational change	Not applicable	Develop an online resource of 'how to implement the rosacea phenotype approach'. This should be freely available, referenceable and accessible. Could integrate with a feedback system (see 'audit and provide feedback', below)
<b>Distribute educational materials</b> (including guidelines, manuals and toolkits) in person, by mail and/or electronically	Not applicable	Develop standard training materials on the new approach for local adaptation and adoption, ideally with endorsement from local or regional associations
<b>Promote adaptability:</b> identify the ways in which a clinical innovation can be tailored to meet local needs and clarify which elements of the innovation must be maintained to preserve fidelity	Global recommendations now exist to consider all skin pigment types when developing tools and diagnostic recommendations <sup>11</sup>	Translate global recommendations and make widely available. Gain feedback from local associations and working groups to identify specific needs
<b>Conduct educational meetings:</b> hold meetings targeted towards different stakeholder groups (e.g. providers, administrators, other organizational groups, and community, patient/consumer and family stakeholders) to teach them about the clinical innovation	Not applicable	Initiate educational meetings targeted to specific groups; could be online or face to face. This should consider information sharing between groups to facilitate an integrated community. Initiate meetings with stakeholders to test-drive implementation tools
<b>Audit and provide feedback:</b> collect and summarize clinical performance data over a specified time period and give them to clinicians and administrators to monitor, evaluate and modify provider behaviour	Not applicable	Develop tools allowing ongoing audit of clinical practice behaviour; could be simple, practical resources for both online and offline use, up to a global clinical registry

Audit and feedback lead to small but potentially important improvements in professional practice.<sup>36</sup> It is therefore important to measure the effectiveness of the phenotype approach as it becomes more widely used, which will both enable sharing of successes to promote a virtuous circle of uptake and identify areas for improvement. In studies assessing the effectiveness of clinical guideline dissemination and implementation, the most widely used strategies for measuring change were medical record audit, computerized databases and health practitioner questionnaire or interview.<sup>37</sup> These align with several recommendations from the World Health Organization to measure specific behaviour change strategies.<sup>38</sup>

The Expert Recommendations for Implementing Change project has compiled a number of implementation strategies for guideline implementation.<sup>39</sup> We have identified those most relevant to the rosacea field and summarized them in Table 2, together with comment on the context of each and potential strategies to measure effectiveness.

Our recommendations are limited by the fact that this is an evolving field of inquiry, meaning future advances may inform modification of signs and symptoms, and subsequent adjustment to our suggested language updates and tools.

Furthermore, even given an objective tool, the severity of some signs can be subjective; for example, some cultures may consider persistent mild centrofacial erythema presenting as 'rosy cheeks' to be a normal or healthy variation. There are also limitations in the use of persistent centrofacial erythema as a definitive diagnostic feature in dark skin phototypes, which will require specific guidance from future work to ensure consistent diagnosis and classification across the patient spectrum.

The transition to a phenotype approach in rosacea is underway; however, there is still significant work to be done to ensure a comprehensive uptake. These practical recommendations are intended to indicate the next steps in this process, with the goals of improving our understanding of the disease, facilitating treatment developments, and ultimately improving care for patients with rosacea.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Appendix S1** Rosacea phenotype checklist.

**Powerpoint S1** Journal Club Slide Set.

**Video S1** Author video.