MR MAX MATOUŠ LOKHORST (Orcid ID : 0000-0001-6369-9195)

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Development of a condition-specific patient-reported outcome measure for measuring symptoms and appearance in vascular malformations: the OVAMA questionnaire

Running head: questionnaire for measuring symptoms and appearance in vascular malformations

M.M. Lokhorst,[1] S.E.R. Horbach,[1] D.A. Young-Afat,[1] M.L.E. Stor,[1] L. Haverman,[2] P.I. Spuls[3] and C.M.A.M. van der Horst[1] on behalf of the OVAMA Steering Group*

*Collaborators OVAMA Steering Group:

F. Blei, MD[4], C.J.M. van der Vleuten, MD PhD[5], I.J. Frieden, MD[6], G.T. Richter, MD[7], S.T. Tan, MD PhD[8], T. Muir, MD[9], A. Penington, MD PhD[10], L.M. Boon, MD PhD[11]

[1]Department of Plastic, Reconstructive and Hand Surgery, Amsterdam University Medical Centers, Amsterdam, The Netherlands

[2]Psychosocial Department, Emma Children's Hospital, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands

[3]Department of Dermatology, Amsterdam University Medical Centers, University of Amsterdam and Amsterdam Public Health, Infection and Immunity, Amsterdam, The Netherlands

[4]Department of Pediatrics, Lenox Hill Hospital, New York, USA

[5]Department of Dermatology, Radboud University Medical Center, Nijmegen, The Netherlands

[6]Department of Dermatology, University of California San Francisco, San Francisco, USA

[7]Department of Otolaryngology, University of Arkansas for Medical Sciences, Arkansas Children's Hospital, Arkansas, USA

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[8]Wellington Regional Plastic, Maxillofacial and Burns Unit, Hutt Hospital, and Gillies McIndoe Research Institute, Wellington, New Zealand

[9]Department of Plastic and Reconstructive Surgery, James Cook University Hospital, Middlesbrough, UK

[10]Department of Pediatrics, University of Melbourne and Murdoch Children's Research Institute, Melbourne, Australia

[11]Center for Vascular Anomalies, Division of Plastic and Reconstructive Surgery, Cliniques Universitaires Saint-Luc, Brussel, Belgium

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Corresponding author: Max M. Lokhorst

Email: m.m.lokhorst@amsterdamumc.nl

What's already known about this topic?

- Vascular malformation symptoms and appearance may severely impact the patient's physical, mental and social functioning
- Condition-specific symptoms and appearance are the main drivers for treatment of vascular malformations
- Symptoms and appearance are determined to be core outcome domains and should be measured in all clinical research on vascular malformations
- No instrument exists for measuring patient-reported symptoms and appearance problems in vascular malformations
- Vascular malformation research is hampered by heterogeneity in outcome measures

What does this study add?

- With this study, a condition-specific patient-reported outcome measure was developed for measuring symptoms and appearance in patients with vascular malformations: the OVAMA questionnaire
- This study confirms adequate content and construct validity

What are the clinical implications of this work?

- Problems that matter most to patients with vascular malformations can now be evaluated from the patients' perspective
- Treatments can be evaluated and compared for effects on these core outcome domains
- This study is a big step in tackling current heterogeneity in outcome measures
- Clinically distinct groups can be determined based on disease severity
- The many applications of the OVAMA questionnaire may significantly improve research, and ultimately, the care for patients with vascular malformations

Summary

Background

The symptoms and appearance of vascular malformations can severely harm a patient's quality of life. The aim of treatment of vascular malformations generally is to improve condition-specific symptoms and/or appearance. Therefore, it is highly important to start testing treatment effects in clinical studies from the patient's perspective.

Objectives

The objective of this study was to develop a patient-reported outcome measure (PROM) for measuring symptoms and appearance in patients with vascular malformations.

Methods

A first draft of the PROM was based on the previously internationally developed core outcome set. The qualitative part of this study involved interviews with 14 patients, which led to a second draft. The second draft was field-tested cross-sectionally, after which groups of items were evaluated for adequate internal consistency (Cronbach's alpha >0.7) to form composite scores. Construct validity was evaluated by testing 13 predefined hypotheses on known-group differences.

Results

The patient interviews ensured adequate content validity and resulted in a general symptom scale with 6 items, head/neck symptom scale with 8 items and an appearance scale with 9 items. Cronbach's alpha was adequate for two composite scores: a general symptom score (0.88) and an appearance score (0.85). Ten out of 13 hypotheses on known-group differences were confirmed, confirming adequate construct validity.

Conclusions

With the development of the OVAMA questionnaire, outcomes of patients with vascular malformations can now be evaluated from the patients' perspective. This may help improve the development of evidence-based treatments and the overall care for patients with vascular malformations.

Introduction

Vascular malformations are congenital deformities, characterized by dilated and tortuous vessels. These benign tangles can occur anywhere in the soft tissues, grow proportionally with the body, and are often visible as a mass differing in colour and texture compared to normal skin. Subtypes are distinguished by the kind of vessel involved: capillary (CM), venous (VM), lymphatic (LM), arteriovenous (AVM) and combined malformations.[1,2]

Clinical presentation varies widely depending on type, localization, extensiveness and involved tissues. Apart from a distorted appearance, patients frequently experience pain, swelling, bleeding, fluid leakage, physical impairment and functional problems.[2-4] These symptoms can severely harm the patient's quality of life, impacting physical, mental and psychosocial well-being.[5] The aim of treatment is generally to improve condition-specific symptoms and quality of life. Treatment can additionally be imperative to preserve or recover vital functions. However, despite the abundance of treatment options, treatment remains challenging as it rarely leads to a complete cure. Many vascular malformations can therefore be seen as a chronic condition, with patients experiencing lifelong symptoms and appearance issues.

A strong contributing factor to current treatment difficulties is the lack of knowledge on the treatments' effect from the *patient's* perspective.[4] Additionally, contemporary evaluation of treatment is impeded by heterogeneous outcome measures.[4,6,7] This hampers the development of evidence-based treatments and treatment guidelines, which are urgently needed to improve outcomes for patients with vascular malformations.

The mission of the Outcome measures for VAscular MAlformations (OVAMA) project is to establish homogeneity in outcome use and reporting. This collaboration includes clinical experts and patient/parent contributors from all over the world. The first step was deciding *what* to measure. In previous studies, the OVAMA collaborative developed a core domain set (CDS) for evaluating treatment in vascular malformations (Figure 1).[8,9] A CDS is a set of outcome domains that should be measured at the minimum when evaluating treatment effect in a certain health condition.[10]

The next step towards homogeneity in outcome use and reporting was determining *how* to measure these core domains. Non-condition-specific domains are advised to be measured by non-condition-specific outcome measurement instruments.[11] However, broadly used instruments such as the Short Form-36 and Skindex-29 seem to fall short for detecting changes in outcome over time in this specific patient population.[12] Newer instruments such as the PROMIS (Patient-Reported Outcomes Measurement Information System[13]) item banks may be used in this patient population as they are more likely to adequately capture small differences in the domains falling under quality of life.[14,15] To fully

capture those domains, the following PROMIS scales were identified: 'pain interference', 'physical functioning', 'anxiety', 'depression' and 'social participation'.

However, no patient-reported outcome measures (PROMs) were available for the patient-reported domain categories 'symptoms', 'anatomy' (including appearance) and 'satisfaction'.[16] We therefore developed a condition-specific PROM to measure vascular malformation symptoms and appearance, called the OVAMA questionnaire. Satisfaction with treatment and outcome is only relevant at follow-up and thus follows a different development process on which we will report in a separate publication ('OVAMA *follow-up* questionnaire'). It is highly important to start testing treatment effect in clinical studies from the patient's perspective since the aim of treatment of vascular malformations is to improve the patient's symptoms or appearance-related issues. Here we report on the development and field-test of the OVAMA questionnaire, measuring symptoms and appearance in vascular malformations.

Methods

The COSMIN (COnsensus-based Standards for the selection of health Measurement Instruments) 'study design for PROMs' checklist was followed for this study.[17] This study adhered to the Declaration of Helsinki, and was exempted from full ethical review by the Medical Ethics Committee of the Amsterdam UMC, since patients were not subjected to interventions or rules of conduct. Informed consent was obtained from all participants. A flowchart of the methods is presented in Supplement 5.

First draft development

Concepts of interest were identified in previous studies.[8,9,16] At first, the literature was searched extensively to determine all outcome domains measured in research on peripheral vascular malformations.[16] Based on these outcome domains, via an international e-Delphi study and two consensus meetings, a CDS was developed wherein outcome domains were defined (Figure 1).[8,9] In total, 167 physicians and 134 patients/parents of younger patients participated to ensure inclusion of the patient's perspective.

No instruments were available for the condition-specific domains falling under 'anatomy', (including 'appearance') and 'symptoms' (including 'pain', 'location-specific symptoms', and 'type-specific symptoms'). Hence, based on these core domains, a first Dutch draft of the OVAMA questionnaire was made with the vascular anomaly expert group of the Amsterdam UMC. It followed the definitions of the domains as determined in the first consensus study and consisted of 5 items on vascular malformation symptoms, 9 items on head/neck symptoms and 7 items on appearance. Symptom items were structured in a way that a patient first answers if they experienced the symptom in the past 4 weeks. If yes, two additional items were presented on frequency and severity, as was determined in the first international consensus study.[8]

Second draft development: concept elicitation and cognitive interviews

Hybrid concept elicitation with cognitive interviews were conducted in patients with vascular malformations. This allowed for immediate matching of emerging concepts of interest to the concepts already included in the first draft.[11] Participants were recruited at the outpatient clinic and from the vascular malformation database of the Amsterdam UMC. Demographic data were collected on age, gender, ethnicity, level of education, type of vascular malformation, lesion localization, lesion size, tissue involvement of lesion, previous treatments. Regarding sample size for the interviews, 5-10 participants were considered sufficient according to a rare disease PROM workgroup and ≥7 according to the COSMIN guidelines.[11,17] At first, 11 patients ≥18 years with a diagnosed peripheral vascular malformation were

interviewed. Secondly, 3 adolescents (age 14-17) were additionally interviewed to evaluate if the concepts of interest were the same and/or if the items were also comprehensible for this age group. We aimed for a heterogeneous group by including at least one of the following subtypes: venous, arteriovenous, lymphatic, capillary, combined; one of the maximal diameter categories: <5, 5-15, 15-30, >30 cm; one of the localization categories: head/neck, upper extremity, trunk, lower extremity; and one of the tissue involvement categories: skin/subcutaneous, muscle, bone. All interviews were conducted by two Medical Doctors, both conducting a PhD on outcome measures in vascular malformations; M.M. Lokhorst (male) and M.L.E. Stor (female). Both were trained in conducting qualitative interviews. A semi-structured interview guide was followed with a standard set of questions.

The first part of the one-on-one, in-person or telephone-based, interviews involved concept elicitation. The interviewer asked open-ended questions to identify the most important problems each patient experiences from their vascular malformation. Further open-ended questions were directed at what patients considered the most important aspects of the spontaneously raised concepts of interest and of the previously established concepts of vascular malformation symptoms (including pain, bleeding, fluid leakage and location-specific symptoms) and appearance.

The second part involved cognitive interviews during which the patients extensively reviewed the draft. Patients evaluated the appropriateness of concepts of interest, domains, items, response options, recall period, and ability to understand the instructions, items and response options. Only the patients in which the head/neck area was affected reviewed the head/neck symptoms scale.

The interviews were then coded by two independent researchers (M.L. and M.S.). All concepts were coded and it was scored if a concept was mentioned by the patient spontaneously, after probing or when reading the questionnaire.

After each interview, recall periods, wording of the items and response options were changed according to relevant patient feedback. All interviews were audio-recorded and transcribed. The version after the last interview was translated to English (using two forward and two backwards translations) and evaluated by the international OVAMA Steering Group, after which the second draft was finished in both Dutch and English.

Field-testing the second draft

The Dutch second draft was distributed among patients who were identified through the vascular malformation database of the Amsterdam UMC. Adult patients and parents of children with a vascular malformation received an invitation by email to complete the questionnaire on the KLIK PROM portal. This is an online secure platform for patients to fill in PROMs and to receive feedback of their scores using

a personal account.[18] Parents of children 14-17 years old were instructed to let the child complete the questionnaire themselves. Parents of children 0-13 years old were instructed to help their child (where needed). The version for children (0-17) only differed from the adult version in form of address (informal and formal). Patients completed the vascular malformation symptom scale, appearance scale and if the head/neck region was affected, also the head/neck symptom scale. If the patients created an account on KLIK but did not fill in the questionnaire, they received a reminder after seven days. Descriptive statistics were analysed for each item individually. All items were scored ordinally. Most items refer to a separate outcome domain and should therefore be evaluated individually. However, we additionally evaluated if groups of items had adequate internal consistency (Cronbach's alpha >0.7) to also form a composite score. Such composite scores may function as a quick indication for disease severity. The following groups of items were analysed: 1. all items from the general symptoms scale, 2. severity and frequency items for every single symptom individually, 3. all items from the head/neck symptoms scale, 4. all items from the appearance scale. If internal consistency was adequate to form a composite score, the scores were converted to a 0-100 scale for easy interpretation (in which higher scores mean more symptom severity).

Construct validity (known-groups validity)

Beforehand, hypotheses on differences in outcome between known-groups were defined (Table 1). Definition of known-groups was based on clinical characteristics (such as lesion localization or maximal diameter as measured with MRI) and clinician-reported outcomes (such as clinician-reported presence of pain in the medical file) from our vascular malformation database. Hypotheses on clinical characteristics were formulated based on common knowledge and patterns we encountered in our database.[1,2,19]

All data were analysed with IBM SPSS (version 26).

Results

Concept elicitation and cognitive interview results

Fourteen patients were interviewed of which the baseline characteristics are shown in Supplement 1. An overview of the interview results is shown in Supplement 2. The interviews showed that pain and appearance were the most relevant concepts according to patients. Bleeding, fluid leakage and several head/neck symptoms were also mentioned spontaneously by patients in the concept elicitation phase of the interview. It became apparent that temporary enlargement of the vascular malformation, which was not yet included, was a major problem for patients. Regarding appearance, most patients thought of the swelling or mass of the lesion as the major aspect of appearance, followed by colour and texture. Additionally, being stared at by other people appeared to be a major problem related to appearance. Patients mentioned that several of these issues were generally not discussed by physicians during regular follow-up, although they are important to their daily functioning.

After probing or during the revision of the questionnaire, all items were noted to be relevant by patients except for problems with the sense of smell. The item on problems with the sense of smell was removed. No further concepts of interest were identified.

The 4-week recall period was deemed the most appropriate by patients, since several symptoms were experienced only once a month, but were considered relevant nonetheless. One patient preferred a recall-period of 6 months, however, this was not considered to be appropriate for measuring and evaluating treatment effect. No patient wished for a shorter recall-period, since several symptoms that were considered relevant for measuring treatment effects occur sporadically or with longer symptom-free periods.

The second draft consisted of a general symptom scale with 6 items, head/neck symptom scale with 8 items and an appearance scale with 9 items (Supplement 3). All responses are scored in ordinal fashion to allow for statistical analysis. For example, items with two options as 1-2, or items with five options as 1-2-3-4-5.

Field-test

A total of 475 patients were invited by email to complete the final concept version. One-hundred-thirty-four patients (28%) completed the questionnaire including 98 adults and 36 children. Baseline characteristics of participants in the field-test are shown in Supplement 3. An overview of the results of the field-test is presented in Supplement 4.

Scoring

Cronbach's alpha was adequate for two composite scores: using the severity and frequency of general problems of vascular malformation items (0.88) and the nine-item appearance scale (0.85). Cronbach's alpha was inadequate for a composite score for the items on pain frequency and severity (0.54), and a composite score for the items on temporary enlargement frequency and severity (0.45). There were too few cases to calculate Cronbach's alpha for a composite score of all items on symptoms, a composite score of frequency and severity of bleeding and fluid leakage or a composite score of all items on head/neck symptoms.

Construct validity (known-groups validity)

An overview of the results of the hypotheses is shown in Table 1. Ten out of 13 hypotheses were confirmed.

Discussion

With this extensive international project, including extensive input from patients and leading clinical experts worldwide, a condition-specific PROM for patients with vascular malformations was developed. The OVAMA questionnaire enables measurement of symptoms and appearance in cross-sectional and prospective research. With the addition of the OVAMA follow-up questionnaire (measuring satisfaction) and the PROMIS scales, this will cover all patient-reported core outcome domains as previously determined by the international vascular malformation community.

International consensus with patients and experts had previously been reached on core outcome domains for measuring treatment effect in vascular malformations. The same domains emerged in our cognitive patient interviews.[8,9] We believe that the participation of patients throughout several steps in the process was essential, and has led to excellent content validity of the PROM according to the COSMIN checklist. By including a clinically representative and heterogeneous group, we incorporated the most common problems for all types of patients with vascular malformations.

The field-test showed that the symptoms of pain and temporary lesion enlargement are common, while bleeding, fluid leakage and head/neck symptoms are rare but relevant nonetheless. As for appearance, the problems seem fairly normally distributed. Since bleeding, fluid leakage and the head/neck symptoms were included in the CDS, and also emerged in the interviews, we decided to keep them in the final instrument. In a later stadium, we may be able to tailor the questionnaire more to the specific characteristics of the patient, so that only questions specifically relevant to that 'type' of patient and lesion are presented to patients. In the current situation, patients who do not experience a certain symptom can skip the frequency and severity items for that symptom.

Construct validity was considered to be good since most known-group hypotheses were confirmed. Results of the three rejected hypotheses were in the expected direction, however, not statistically significant. Furthermore, this concerned small subgroups, thus the hypotheses may potentially be confirmed with an increased sample size in future studies. Formulation of hypotheses was limited since there is a paucity of knowledge on what clinical characteristics determine disease and symptom severity, and appearance problems. One of the goals of the OVAMA questionnaire is to investigate such clinical patterns and thereby define clinically distinct groups, which will also be evaluated in future studies.

The e-Delphi study and consensus meetings involved both adult patients and parents of children with vascular malformations. Thus, the core domains pertain for both groups, making the questionnaire suitable for both adults and children, and allowing for comparison between groups.

Below the age of 8, it is generally advised to let parents fill in questionnaires.[20] Since one of the main goals of the OVAMA project is to increase comparability, we chose to let parents fill in the PROM for

patients up to 14 years, instead of developing a separate PROM for children between the ages of 8 to 14. This this would have resulted in two different PROMs and comparison would then be impossible.

Scoring

The ordinal rating of the response options allows for statistical analysis. Since most items refer to a separate outcome domain, the *individual* item outcome is relevant. All items should be analysed and reported separately. Additionally, two composite scores can be calculated reliably: general problems and appearance. These scores will quickly give the clinician or researcher an idea of disease severity. Subsequent evaluation of the individual items will then reveal specifically what causes the severity. However, for evaluating treatment effect, we urge to only evaluate changes in the *individual* items, since the composite scores are still rough, and clinically important changes can occur in separate symptoms or aspects of appearance. In the future, after refining the scoring model based on more data, it could potentially become possible to form additional composite scores for other symptoms.

We chose to develop a questionnaire for *all* patients with vascular malformations for several reasons. Currently, there is little evidence of what problems are subtype-specific. With this questionnaire, we can compare the presence and severity of symptom and appearance problems *between* the different subtypes, which will provide evidence on what problems are more relevant for the specific subtypes. Also, the lesions are often of combined origin, clinical diagnoses show discrepancy with histopathological diagnoses, and future classification is likely to change based on genetic mutations.[21]

In this study, we interviewed 14 patients and reached saturation, so we consider this sample to be adequate for draft development. In contrast, the response rate of the field-test was low in certain subgroups but adequate for the overall group. A large group of eligible patients were treated years ago. Such patients may not have felt prompted to participate. However, we believe that by avoiding a selection of certain patients of our database, we were able to investigate a relatively large representative sample size which reflects the whole group in the best possible way.

The OVAMA questionnaire will be freely available online (www.ovama.org) to stimulate wide use. The final version is available in Dutch and English, after it was translated into English following the COSMIN linguistic validation standards.[17] A protocol for translation to other languages is being developed, enabling easy and correct translation by local groups independently.

The OVAMA questionnaire will allow us to tackle the current heterogeneity in outcome measures within the field of vascular malformations and thereby allow for comparison of treatments. This PROM allows us to identify which treatment options affect which specific symptom or appearance problem.

Treatments can then be tailored more to the individual patient, since the clinician has more scientific evidence at hand on how treatments affect certain subgroups or specific symptoms differently. This is especially important in this heterogeneous patient group. Additionally, the OVAMA questionnaire enables definition of clinically distinct groups, which allows for classification on disease severity based on the severity of symptoms and appearance problems. This is even more pressing with the emerging gene-targeted therapies, which will predominantly play a role in more severe cases, for which a proper definition is currently lacking.

To conclude, with the development of the OVAMA questionnaire, problems that matter most to patients with vascular malformations can be studied scientifically. The many applications of the OVAMA questionnaire may significantly improve research, and ultimately, the care for patients with vascular malformations.

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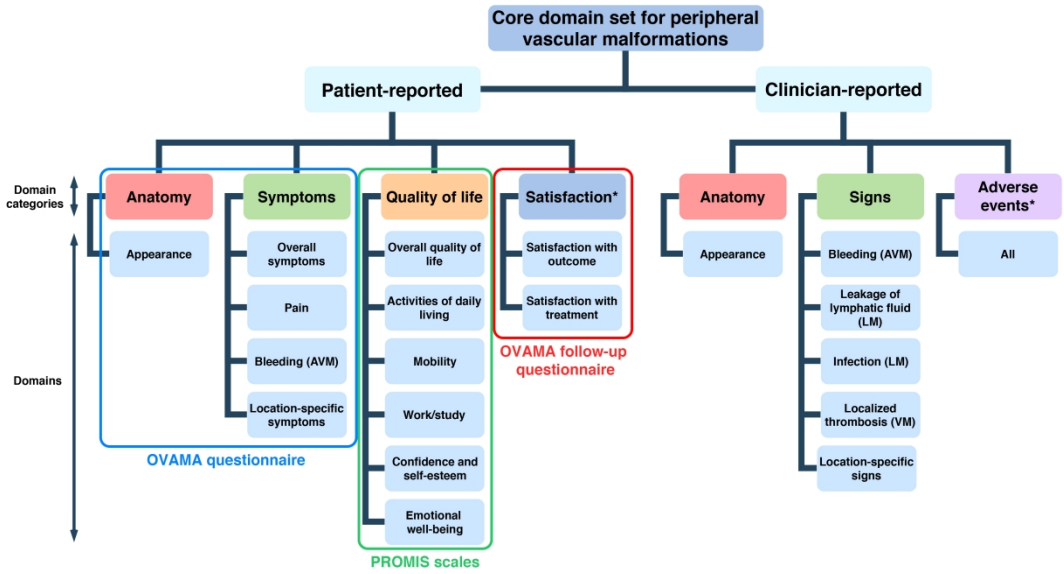
Figure legends

Figure 1. Core domain set for vascular malformations. AVM = arteriovenous malformation, LM = lymphatic malformation, VM = venous malformation.

Supplement 5. Flowchart of the methods. *Will be reported in a separate study.

Table 1. Hypotheses on known-group differences. NA = not applicable.

	Hypothesis	Group size	Result	Confirmation
1	Higher presence of pain in patients with *clinician*-reported (medical history of) pain	80 vs 54	73% vs 20% (p<0.000)	Confirmed
2	Higher presence of pain in patients with intramuscular lesions	61 vs 73	69% vs 37% (p<0.000)	Confirmed
3	Higher presence of pain in patients with lower extremity lesions	48 vs 86	67% vs 43% (p=0.009)	Confirmed
4	Higher presence of bleeding in patients with *clinician*-reported (medical history of) bleeding	22 vs 111	23% vs 6% (p=0.013)	Confirmed
5	Higher presence of fluid leakage in patients with lymphatic component	19 vs 115	16% vs 3% (p=0.025)	Confirmed
6	Higher presence of temporary lesion enlargement in patients with venous or lymphatic component	96 vs 38	68% vs 38% (p=0.001)	Confirmed
7	High correlation (>0.5 Spearman's rho) between clinician-reported lesion size and patient-reported lesion size	134	Spearman's rho: 0.558	Confirmed
8	Less swelling/mass in patients with *pure* capillary malformations	13 vs 121	2.08 vs 2.69 (p=0.079)	Rejected
9	Less color difference with skin in patients with *pure* lymphatic malformations	13 vs 121	2.00 vs 2.88 (p=0.053)	Rejected
10	More color difference with skin in patients with skin/subcutaneous tissue involvement	109 vs 25	3.09 vs 1.48 (p<0.000)	Confirmed
11	More texture difference with skin in patients with skin/subcutaneous tissue involvement	109 vs 25	2.54 vs 2.08 (p=0.14)	Rejected
12	More facial distortion in patients with head and neck lesions	55 vs 79	2.58 vs 1.15 (p<0.000)	Confirmed
13	More bodily distortion in patients with arm, trunk and leg lesions	86 vs 48	2.65 vs 1.38 (p<0.000)	Confirmed



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