


# BMJ Open Optimisation of Diagnostic Accuracy in idiopathic inflammatory myopathies (ADAPT study): a protocol for a prospective diagnostic accuracy study of multimodality testing in patients suspected of a treatable idiopathic inflammatory myopathy

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## ABSTRACT

**Introduction** Idiopathic inflammatory myopathies (IIMs) excluding inclusion body myositis (IBM) are a group of heterogeneous autoimmune disorders characterised by subacute-onset and progressive proximal muscle weakness, which are frequently part of a multisystem autoimmune disorder. Reaching the diagnosis can be challenging, and no gold standard for the diagnosis of IIM exists. Diagnostic modalities include serum creatine kinase activity, muscle imaging (MRI or ultrasound (US)), electromyography (EMG), myositis autoantibody testing and muscle biopsy. Several diagnostic criteria have been developed for IIMs, varying in reported sensitivity and specificity.

**Hypothesis** We hypothesise that an evidence-based diagnostic strategy, using fewer and preferably the least invasive diagnostic modalities, can achieve the accuracy of a complete panel of diagnostic tests, including MRI, US, EMG, myositis-specific autoantibody testing and muscle biopsy.

**Methods and analysis** The Optimisation of Diagnostic Accuracy in idiopathic inflammatory myopathies study is a prospective diagnostic accuracy study with an over-complete study design. 100 patients suspected of an IIM excluding IBM will be included. A reference diagnosis will be assigned by an expert panel using all clinical information and all results of all ancillary tests available, including 6 months of follow-up. Several predefined diagnostic strategies will be compared against the reference diagnosis to find the optimal diagnostic strategy.

**Ethics and dissemination** Ethical approval was obtained from the medical ethics committee of the Academic Medical Centre, University of Amsterdam, The Netherlands (2019-814). The results will be distributed through conference presentations and peer-reviewed publications.

## Strengths and limitations of this study

- Comparative evaluation of a complete panel of diagnostic modalities to assess the incremental value of multitest diagnostic strategies in idiopathic inflammatory myopathies.
- Blinded evaluation of individual diagnostic tests.
- Limited power for subgroup analyses.

**Trial registration number** Netherlands trial register; NL8764.

## INTRODUCTION

Idiopathic inflammatory myopathies (IIMs), often called ‘myositis’, are a group of heterogeneous autoimmune disorders characterised by subacute-onset and often severe, progressive proximal muscle weakness. IIMs encompass four treatable subgroups: dermatomyositis (DM), antisynthetase syndrome (ASS), immune-mediated necrotising myopathy (IMNM) and non-specific/overlap myositis (OM).<sup>1</sup> Since inclusion body myositis (IBM) is not amenable to treatment, it is not within the scope of this study. First-line treatment usually consists of glucocorticoids. Besides the typical proximal muscle weakness, dysphagia is often present, and extramuscular manifestations may occur in IIMs and may be the initial symptom, for example, a skin rash, interstitial lung disease (ILD), connective tissue disease or cardiomyopathy.

The clinical symptoms and signs differ widely between patients at disease onset and reaching a correct diagnosis in a timely manner can be challenging.<sup>2</sup>

There is no gold standard for the diagnosis of IIM. Diagnostic modalities include standard laboratory testing (serum creatine kinase (sCK) activity, lactate dehydrogenase (LDH), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and aldolase), muscle imaging via MRI or ultrasound (US), electromyography (EMG), myositis autoantibody testing and muscle biopsy. Evaluations of a range of diagnostic strategies have resulted in divergent sensitivities and specificities for the individual diagnostic modalities.<sup>1 3–6</sup> Relatively new modalities, such as myositis-specific autoantibody (MSA) testing and US, seem promising.<sup>7–9</sup>

Although the diagnostic accuracy of some of the above-mentioned tests has been studied before,<sup>7 10–12</sup> to the best of our knowledge, no previous study has examined a complete diagnostic panel for myositis. A prospective, comparative diagnostic accuracy study with an over-complete study design enables the evaluation of the diagnostic accuracy of individual items and procedures and of the incremental value of multitest diagnostic strategies. We hypothesise that an evidence-based diagnostic strategy, using fewer and preferably the least burdensome diagnostic modalities, can achieve the accuracy of the complete panel of diagnostic tests, which includes MRI, US, EMG, MSA testing and muscle biopsy.

## Aim

The primary aim of this study (ADAPT—OptimizAtion of Diagnostic Accuracy in idioPathic inflammaTory myopathies) is to identify a diagnostic strategy with an optimal accuracy for patients suspected of an IIM who need treatment with glucocorticoids, by comparing the accuracy of a range of strategies against a panel-based reference diagnosis, based on all available information and follow-up data.

## METHODS AND ANALYSIS

### Study status

Recruitment of study participants started on 16 June 2020. The expected end date of this study is September 2023, when all included patients will have completed their follow-up visit. This project has been registered in the Netherlands Trial Register.

### Study design

The ADAPT study is a prospective, fully paired diagnostic accuracy study, with an over-complete diagnostic design for patients suspected of having IIM. This means that all consenting participants undergo standardised history taking, physical examination, standard laboratory testing (including sCK), muscle imaging by whole body muscle MRI and muscle US, EMG, myositis autoantibody testing and muscle biopsy. The clinical reference standard is the

final diagnosis assigned by an expert panel with all clinical information available, including 6 months of follow-up.

### Participants

This study is a single-centre study. The Amsterdam University Medical Centre serves as a tertiary referral centre for IIM in the Netherlands. Potentially eligible patients are recruited according to the following inclusion and exclusion criteria. Eligible patients who refuse any of the diagnostic tests of the study protocol will not be included.

### Inclusion criteria

To be eligible, a patient must be suspected of an IIM based on symptoms and signs:

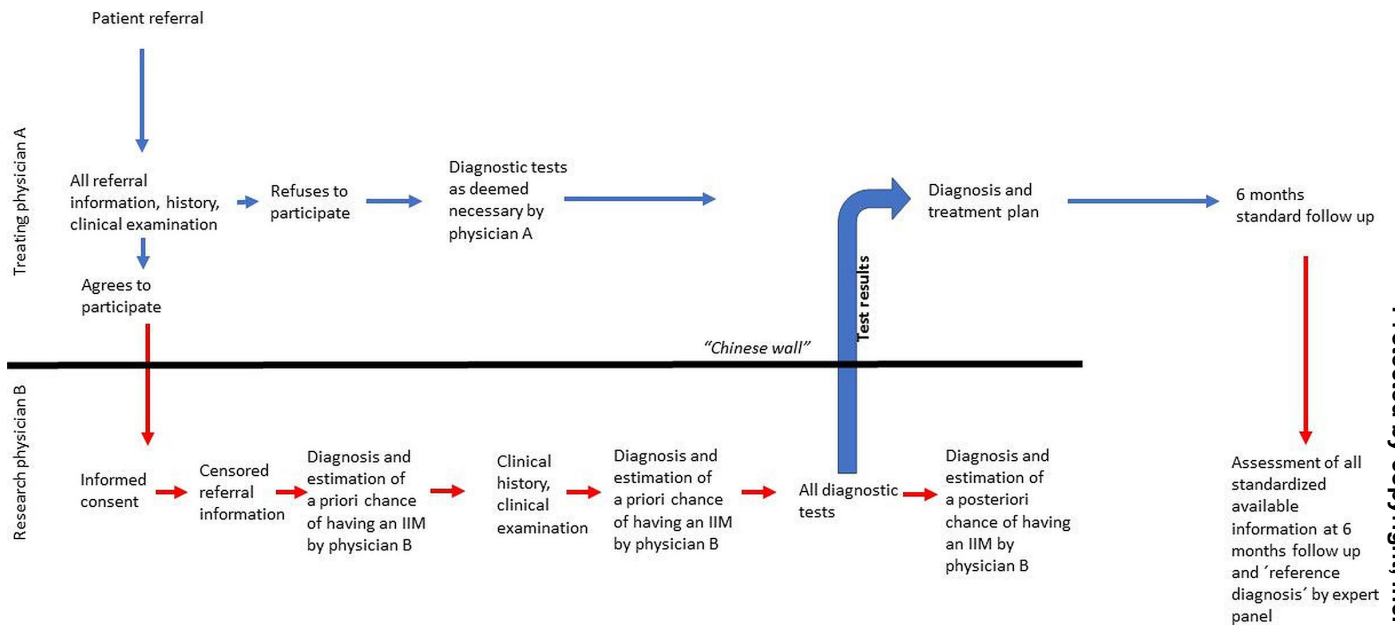
- ▶ Symmetrical proximal muscle weakness causing a functional limitation that justifies treatment with high-dose glucocorticoids\*.
- ▶ Onset of symptoms  $\leq 24$  months before inclusion.
- ▶ In case of DM with classical skin lesions: additional informed consent for muscle biopsy.
- ▶ Age of 18 years and older.

\* Patients with a connective tissue disorder and/or cancer are eligible

### Exclusion criteria

- ▶ Alternative cause for proximal muscle weakness, for example, the use of myotoxic medication (with the exception of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) inhibitors), a positive family history for a hereditary neuromuscular disease or known inflammatory or infectious causes for myopathy outside the spectrum of IIM (eg, graft versus host disease or sarcoidosis).
- ▶ A high suspicion of sporadic IBM based on clinical symptoms, for example, the combination of slow onset of asymmetrical, weakness of quadriceps and deep finger flexor muscles, dysphagia and age  $> 50$  years.<sup>2</sup>
- ▶ High suspicion of a neurogenic disease, based on a neurological examination showing more severe distal weakness than proximal weakness, asymmetric weakness, distal muscle atrophy or fasciculations.
- ▶ Follow-up up to 6 months not possible.
- ▶ To avoid an effect of immunosuppressive treatment on results of diagnostic tests, patients with immunosuppressive treatment within the last 3 months prior to screening are excluded, with the exception of:
  - Oral prednisone  $\leq 60$  mg/day since 1 week, without clinical response\*.
  - Oral prednisone  $\leq 20$  mg/day since 2 weeks, without clinical response\*.
  - Steroid sparing agents (eg, methotrexate, azathioprine, mycophenolate mofetil) when prescribed less than 4 weeks prior to screening, without clinical response\*.
- ▶ History of IIM.
- ▶ Contraindication for MRI.

\*The presence or absence of a clinical response will be judged by the treating physician.



**Figure 1** Study structure, describing the patient journey and roles of physician A and B and the expert panel.

**Subscript:** The 'Chinese wall' represents the blinding of research physician B from all information about the patient that is not related to the study as long as probability scores are given. IIM, idiopathic inflammatory myopathy.

### Ethics and informed consent procedure

The study protocol has been approved by the medical ethics committee of the Academic Medical Centre, Amsterdam, The Netherlands. Potentially eligible patients are informed about the study via a telephone call and study information is sent by (e)mail. A physical examination is performed by the treating physician A (see below) as a screening before the consent procedure.

### Study structure

The study structure is presented in figure 1.

### Study procedures

On inclusion, the International Myositis Assessment and Clinical Studies (IMACS) outcome assessment tool<sup>13</sup> is filled out by the patient and treating physician, including all six core set measures: physician global activity, patient global activity, Manual Muscle Testing (MMT), Health Assessment Questionnaire, muscle enzyme levels and extra muscular disease activity based on the Myositis Disease Activity Assessment Tool.

### Blinding of physicians

All study-related neurological examinations are performed by research physician B, who is blinded from diagnostic results. The patient is diagnosed and treated, as part of regular care, by physician A. Both physicians are experienced neuromuscular specialists with expertise in IIM.<sup>14</sup>

### Censoring of referral letter

Referral letters are censored for physician B unto the following essential information: medical history, physical and neurological examination and standard laboratory

investigations (electrolytes, sCK, LDH, ASAT, ALAT, aldolase).

### Medical history taking and neurological examination

A standardised medical history is taken and structured neurological examination performed including signs of extramuscular disease activity by physician B, that is, assessment of cutaneous abnormalities, calcifications, signs of arthralgia or arthritis, dyspnoea and MMT<sup>15</sup>: neck flexors and extensors and bilaterally: trapezius, deltoid, biceps brachii, gluteus maximus, gluteus medius, iliopsoas, hamstrings, quadriceps, wrist extensors, wrist flexors, ankle dorsiflexors and ankle plantar flexors and additionally triceps brachii and deep finger flexors.

### Diagnostic tests

The complete panel of diagnostic tests is performed according to the description below.

### A study-related follow-up visit

After 6 months, a study-related follow-up visit is used to collect the following data: disease course during the past 6 months, that is, change of symptoms and signs, occurrence of remission or relapse, use of immunosuppressive or immunomodulatory and other medication, final diagnosis according to current diagnostic criteria of the treating physician, alternative neuromuscular diagnosis and concomitant extramuscular manifestations (eg, other autoimmune disorder, malignancy, cardiomyopathy, ILD). The core set measures of the Total Improvement Score (TIS) of the IMACS will be collected again, which enables calculation of the TIS.<sup>16</sup>



## Expert panel

All available clinical information and research data are provided in a standardised way to a panel of experts in the field of neuromuscular disorders: original referral letters, censored referral letters, medical history and neurological examination, results of all ancillary investigations, and the disease course during 6 months after diagnosis.

First, panel members evaluate cases individually, after which consensus is aimed for in a group discussion. The expert panel diagnosis for each patient serves as the clinical reference standard in evaluations of the accuracy and incremental accuracy of individual diagnostic tests and testing strategies. The panel will use criteria to achieve consistency and acceptable reproducibility.

## Diagnostic tests

### Whole-body muscle MRI

Patients undergo a standardised 3.0 Tesla Whole body muscle magnetic resonance imaging (Philips, Best, The Netherlands), which includes water and fat imaging on T2-weighted 2-point Dixon axial 2D scans. Axial planes through shoulder region, upper limbs, hip region, mid-upper leg and mid-lower leg region are performed. Additional coronal T2 mDixon images of the thighs are performed to allocate the biopsy location.

### Ultrasound

US examination is performed by an experienced clinical neurophysiologist, using a Esaote MyLabTwice US scanner with an 8–14 MHz broadband linear transducer with a 53 mm footprint and an axial resolution of around 0.2 mm (Esaote SpA, Genoa, Italy). Nine muscles are examined bilaterally: deltoid, biceps brachii, flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, rectus femoris, vastus lateralis, tibialis anterior and gastrocnemius muscles. The neurophysiologist analyses every single muscle semiquantitatively using the 4-point Heckmatt grading scale<sup>17</sup> and visually by examination of the echo intensity, calcifications and focal abnormalities.

### Electromyography

Needle-EMG is performed by an experienced clinical neurophysiologist, being a different person than the US evaluator. Ten muscles are tested unilaterally: deltoid, biceps brachii, flexor carpi radialis, flexor digitorum profundus, iliopsoas, vastus medialis, gluteus maximus, tibialis anterior and gastrocnemius (lateral head) and one paraspinal muscle at level L3.<sup>18 19</sup> EMG is performed after muscle imaging, in order to avoid misinterpretation of damage due to needle insertion for inflammatory abnormalities.

## MSAs and myositis-associated antibodies

Antibodies are analysed in serum using the EURO-line myositis 16 Ag. line-blot assay and the EUROline ANA Profile 5 line-blot assay of Euroimmun (Lübeck, Germany). Antibodies against HMGR are analysed with a quantitative ELISA (Inova, San Diego, California). The presence of the following MSAs will be detected: antibodies against SRP, EJ, OJ, Mi-2 $\alpha$ , Mi-2 $\beta$ , TIF1- $\gamma$ , MDA5, NXP2, SAE1, PL-12, PL-7, Jo-1 and HMGR and the following myositis-associated antibodies (MAAs): antibodies against Ku, RNP (70, A and C), PM/Scl-75 and PM/Scl-100 and anti-Ro52.<sup>20</sup> The presence of an antibody is scored negative (–), weakly positive (+), positive (++) and strongly positive (+++) by an experienced immunologist.

Antinuclear antibody testing is performed simultaneously and the results of nuclear and cytoplasmatic Hep2 indirect immunofluorescence staining (Euroimmun) will be used as a verification of the presence of autoantibodies, where applicable.

### Muscle biopsy

The optimal biopsy site is based on the presence of oedema on muscle MRI, as indicated by the radiologist and the treating physician. If no oedema is present, the biopsy is taken from a clinically weak muscle. The biopsy is taken according to recommended standards for muscle biopsies.<sup>21</sup>

## Evaluations of diagnostic tests

The evaluating clinical neurophysiologist (n=2), radiologist (n=2), immunologist (n=2) and pathologist (n=1) are blinded from the contents of the censored referral letter, results of medical history and neurological examination and results of the other diagnostic modalities. Participants are kindly asked not to speak about any known results to the research physician and evaluators of the diagnostic tests. The diagnostic tests are evaluated using standard methods used in clinical practice. For MRI, the imaging assessment is performed by two musculoskeletal radiologists who should reach consensus. The test result—the probability of an IIM based on the diagnostic test—is expressed on a 5-point Likert scale (low to high probability) by the evaluator (figure 2). For myositis autoantibodies, the test results are given as follows: certainly not: all antibodies negative; probably not: any positivity of Ro52 and/or MAA+; uncertain: MSA+; probably yes: MAA ++ or +++; certainly yes: MSA ++ or +++. For the muscle biopsy, an experienced neuropathologist, specialised in the field of muscle diseases, decides whether the

The results of [XX diagnostic modality] are consistent with diagnosis idiopathic inflammatory myopathy

Certainly not ☐ Probably not ☐ Uncertain ☐ Probably yes ☐ Certainly yes ☐

**Figure 2** Form for every diagnostic modality filled in by the evaluator of the diagnostic test.

Based on [1] the referral letter/ 2) the referral letter and medical history + neurological examination+ laboratory results/ 3) the referral letter, medical history + neurological examination, laboratory results and results of the diagnostic tests], I diagnose an IIM...

Certainly not      Probably not      Uncertain      Probably yes      Certainly yes

☐                      ☐                      ☐                      ☐                      ☐

**Figure 3** Form after diagnostic testing filled in by physician B.

findings are compatible with an IIM according to international criteria.<sup>22 23</sup>

### Probability of IIM diagnosis

In different phases of the study, research physician B assigns a probability of an IIM diagnosis. In addition, evaluators of the diagnostic tests and the expert panel assign a probability of an IIM diagnosis. These phases are explained below.

Phase 1: probability before additional testing.

Step 1: physician B assigns the a priori probability of a diagnosis of IIM on a 5-point Likert scale based on the censored referral letter.

Step 2: physician B assigns a second a priori probability of a diagnosis of IIM on a 5-point Likert scale based on the information of the censored referral letter, his/her standardised medical history and neurological examination and laboratory tests.

Phase 2: probability of additional diagnostic testing (figure 3).

Step 3: each evaluator of a diagnostic test evaluates whether the findings of their particular diagnostic modality are compatible with an IIM and assigns a probability score on a 5-point Likert scale.

Step 4: physician B assigns the a posteriori probability of an IIM diagnosis on a 5-point Likert scale, based on all available information of steps 1–3 (censored referral letter, standardised medical history, neurological examination, laboratory results and results of each evaluator of a diagnostic test).

Phase 3: probability by expert panel (reference diagnosis).

Step 5: The expert panel first assigns its probability of a diagnosis of IIM on a 5-point Likert scale, and, second, whether the available information allows for a more specific (sub)diagnosis (DM, ASS, IMNM and OM). The 5-point Likert scale gives the reference panel the opportunity to express uncertainty.

### Patient burden

Patient burden is evaluated using a questionnaire. For each diagnostic modality, study participants are invited to rate the experienced burden on a 4-point Likert scale, anchored at 4=very burdensome, 3=fairly burdensome, 2=somewhat burdensome or 1=no burden at all. These data will be used to compare the burden of different combinations of diagnostic tests.

### Sample size

We expect to include two patients per month in this study and aim to recruit 100 patients, of whom 60% is expected to have an IIMs that needs glucocorticoid treatment. Two previous studies substantiate this expectation with a mean ‘IIM’ percentage of 62% and ‘no IIM’ percentage of 37%.<sup>12 24</sup> This sample size would allow us to provide a CI from 80% to 96% around an expected sensitivity of 90% in assigning a correct IIM diagnosis, and from 87% to 100% around an expected specificity of 97%.<sup>25</sup>

### Statistical analysis

In the statistical analysis, the focus will be on the incremental accuracy of diagnostic tests over the censored referral letter, standardised medical history, physical examination and basic laboratory findings. First, all probability scores on the 5-point Likert scales will be dichotomised: options ‘certainly not’, ‘probably not’ and ‘uncertain’ will be categorised as ‘No IIM’. Options ‘probably yes’ and ‘certainly yes’ will be categorised as ‘IIM’. Estimates of diagnostic accuracy—sensitivity, specificity and positive and negative predictive values—will be calculated for the following:

#### Diagnostic accuracy of medical history, neurological examination, basic laboratory findings and diagnostic tests

For every single patient, the a priori and a posteriori probability diagnosis of physician B will be compared against the final diagnosis assigned by the expert panel. The difference in diagnostic accuracy between a priori and a posteriori probability will show the incremental accuracy of medical history, neurological examination and basic laboratory findings and diagnostic tests relative to the information in the referral letter.

#### Diagnostic accuracy of the single diagnostic tests

The diagnostic accuracy of the single test modalities will be calculated by comparing the results of the individual diagnostic test (scores assigned by the evaluator) against the final diagnosis assigned by the expert panel. We will use the McNemar test<sup>26</sup> to compare the sensitivities and specificities between single diagnostic tests. Since whole-body muscle MRI may not be routinely available in all hospitals, a subanalysis using the MRI of the thighs only will be performed.

## Diagnostic accuracy of diagnostic strategies

The accuracy of diagnostic strategies, based on combinations of diagnostic tests, will be calculated. For every diagnostic strategy, estimates of sensitivity, specificity and predictive values will be calculated. We will start by comparing strategies built with the following items: medical history ( $H_x$ ), physical examination (Physical Ex), laboratory results (Lab), MRI, US, EMG, antibodies (Ab), muscle biopsy (Muscle  $B_x$ ) \*

1. [ $H_x$ , Physical Ex, Lab].
2. [ $H_x$ , Physical Ex, Lab]+Ab-pos.
3. [ $H_x$ , Physical Ex, Lab]+Abpos+MRI.
4. [ $H_x$ , Physical Ex, Lab]+Abpos+US.
5. [ $H_x$ , Physical Ex, Lab]+Abpos+EMG.
6. [ $H_x$ , Physical Ex, Lab]+Abneg + [MRI+ $B_x$ ].
7. [ $H_x$ , Physical Ex, Lab]+Abneg+US + [MRI+ $B_x$ ].
8. [ $H_x$ , Physical Ex, Lab]+Abneg+EMG + [MRI+ $B_x$ ].
9. [ $H_x$ , Physical Ex, Lab]+Abneg+EMG+US + [MRI+ $B_x$ ].

\* It will be taken into account that the muscle biopsy is dependent on imaging, since the biopsy location is MRI guided.

## Comparing diagnostic strategies

The guiding principle in the analysis will be that we will compare diagnostic strategies in terms of their accuracy and cumulative burden. The burden related to procedures will be based on the mean reported burden in the questionnaires. The total burden of a diagnostic strategy will be evaluated as the cumulative burden score of the different tests. We will rank the strategies in terms of their sensitivity and list the corresponding specificity, predictive values and patient burden with 95% CIs. Dominated strategies, that is, strategies with a higher burden without providing better sensitivity or specificity, will then be eliminated from the ranking, if differences are statistically significant. In addition, we will explore the use of decision curves, based on net benefit analysis, to highlight the comparison of the remaining diagnostic strategies.<sup>27</sup>

## Missing data

Inconclusive diagnostic test results will be treated as negative in the calculation of the diagnostic accuracy. Results are considered inconclusive if no probability diagnosis is made by the evaluator. If two or more diagnostic tests of the same patient are missing, the expert panel might decide that a reference diagnosis cannot be assigned to that particular patient, which will result in exclusion from the analysis. We anticipate very few missing data due to structured planning of the diagnostic tests.

## ETHICS AND DISSEMINATION

The study will be conducted according to the principles of the Declaration of Helsinki (V.Fortaleza Brasil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (Wet maatschappelijke ondersteuning (WMO)). Data management, monitoring and reporting of the study will be performed

in accordance with the International conference on harmonisation for good clinical practice (ICH GCP) guidelines.

The results will be distributed through conference presentations and peer-reviewed publications.

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**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Consent obtained directly from patient(s)

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