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Long-term prognosis, treatment, and outcome of patients with fever of unknown origin in whom no diagnosis was made despite extensive investigation

A questionnaire based study

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Abstract
In 30–50% of patients with fever of unknown origin (IUO) no explanation for the fever can be found. Prognosis and effects of empirical treatment of these patients are largely unknown.

With this retrospective, questionnaire based cohort study in all unexplained FUO patients in an expert center between 2003 and 2014 we studied mortality and outcome.

In 131 of 274 FUO patients, FUO remained unexplained. Ninety-nine of them responded to the long-term follow up questionnaire. After a median duration of follow-up of 60 months, spontaneous remission of fever occurred in 47.3%. Empirical treatment was effective in 66.7% of patients. Mortality was 6.9%. The cause of death was considered not to be related to the febrile disease in five out of six patients. Ten out of 99 responders reported to have received a final explanation for FUO after evaluation in the expertise center, but this diagnosis could not be confirmed in six cases and was considered to be an unlikely explanation for FUO in four out of six cases.

We conclude that mortality in unexplained FUO is low and mostly unrelated to the febrile disease. Spontaneous resolution of fever is common. Empirical treatment prescribed by an expert physician is often effective, but should be avoided until all diagnostic possibilities have been exhausted.

Abbreviations: FUO = fever of unknown origin, IUO = inflammation of unknown origin.

Keywords: fever of unknown origin, mortality, prognosis, survival, therapy, treatment

1. Introduction
Fever of unknown origin (FUO) and inflammation of unknown origin (IUO) are complex diagnostic problems encountered by many different medical specialists. FUO/IUO is defined as at least 3 weeks duration of fever or elevated inflammatory markers in an immunocompetent patient, for which no cause is found despite an extensive workup.\textsuperscript{[1–4]} (Table 1).

In recent Dutch and other western-European cohorts,\textsuperscript{[1,5–9]} 30% to 50% of patients remain undiagnosed despite extensive evaluation. The prognosis of these patients is not well known. The only western-European study specifically designed to determine the prognosis of FUO patients reported a mortality of 2.4% in 168 undiagnosed patients. In that study, all deaths in patients with unexplained FUO occurred during the index admission.\textsuperscript{[10]}

Although spontaneous resolution of FUO was reported in 43% to 75% of undiagnosed cases\textsuperscript{[1,3,6,11]}, many patients with undiagnosed FUO are empirically treated with antibiotics, corticosteroids, or other anti-inflammatory drugs. The effects of these treatments are largely unknown.

We performed a questionnaire-based long-term follow-up study on treatment and prognosis in patients with FUO that remained undiagnosed during the 2 most recent Dutch FUO studies.\textsuperscript{[1,9]}

2. Materials and methods
2.1. Patient selection
All patients that remained undiagnosed in the 2 most recent Dutch FUO studies were eligible for inclusion. Both studies were performed in the Radboud university medical center, a 630-bed tertiary referral center and expertise center for FUO. These 2 studies included 245 patients with FUO and 64 patients with IUO. Inclusion criteria are described in detail elsewhere.\textsuperscript{[1,9]}

2.2. Medical ethics approval
This study was assessed by the medical ethics committee Arnhem-Nijmegen (registration number 2014/309) and according to
Dutch law it was exempt from approval and the collection of written informed consent because of its non-invasive design and anonymous storage of patient data.

2.3. Data collection
2.3.1. Medical records. Demographic data and data on FUO, including age of onset, date of first presentation, fever pattern, treatment, outcome, and survival were collected from the medical records.

2.3.2. Surveys. Eligible patients were contacted by phone. A standardized interview (English translation in Supplement 1, http://links.lww.com/MD/C308) was performed. If calls remained unanswered, a standardized questionnaire including the same questions as the telephonic interview was sent out either by regular mail or email. A prepaid pre-addressed return envelope was included in all surveys sent out by regular mail. E-mails contained a hyperlink to a secured online survey. Patients that did not complete the survey within 2 weeks were sent a reminder. Online survey responses were only included in the analyses if they were fully completed.

If patients reported to have visited another hospital because of FUO or IUO after the end of the FUO study, they were asked permission to approach the health-care provider to collect relevant medical data. If patients gave consent, they were sent a paper informed consent form and prepaid pre-addressed return envelope. These forms were used to collect relevant medical data from other hospitals. The proof of the diagnosis and the likelihood of being related to FUO were discussed between all investigators for all final diagnoses until consensus was reached. Diagnoses were categorized as confirmed when considered sufficiently validated based on the collected data. If insufficiently proven, diagnoses were categorized as unconfirmed.

Patients had not been instructed to regularly measure their body temperature, but did so on their own initiative. Continuous fever or inflammation was considered cured if patients had been fever or symptom free for at least 1 week at the time of the questionnaire. Recurrent fever or inflammation was considered cured based on the individual fever or inflammation pattern. If any information on remission of fever or inflammation was unclear, it was discussed between the investigators until consensus was reached.

For patients responding to the questionnaire, duration of follow up was defined as the time between the first presentation to the Radboudumc and the date on which the questionnaire was completed. For non-responders, duration of follow up was defined as the interval between the first presentation and the last contact with the Radboudumc during the FUO study.

2.4. Statistical analysis
Categorical data are represented as number (percentage) and compared by Fisher exact test. Continuous data are represented as median (range) and compared using two-tailed Mann–Whitney U test. A P-value of <.05 was considered statistically significant. Statistical analyses were performed using SPSS for Windows, version 22.0 (IBM, Armonk, New York).

3. Results
3.1. Patient characteristics
The 2 most recent Dutch cohort studies on FUO/IUO included a total of 274 patients, in 131 (47.8%) of which the cause for the fever or inflammation remained unknown. Sixty-three patients with unexplained FUO (48.1%) were men. Total median duration of follow up was 60 months (range, 0–177 months). (Table 2).

3.2. Prognosis during FUO study
3.2.1. Treatment during FUO study. Median duration of follow-up during both FUO studies was 18 months (range, 0–58 months). Fifty-three of the 131 patients with unexplained FUO (40.5%) were treated during the FUO studies. Steroids and drugs in the category other drugs were the most commonly used (N=26, 19.8%) (Table 3).

Of all 53 patients that received at least 1 treatment for unexplained FUO during the FUO study, 11 (20.6%) did not respond to the questionnaire. Remission of fever upon treatment was noted in the medical chart in 4 of them (36.6%).

Of the 71 patients that remained untreated during the FUO study, 11 (15.4%) did not respond to the questionnaire. In 7 of these patients (63.6%) spontaneous remission of fever was noted in the medical charts. Median duration of fever in these patients was 3.5 months (range 0–38 months).

3.2.2. Survival. Three patients (2.3%) died during the FUO studies. The cause of death remained unknown in 1. The 2 other patients died of heart failure, which was regarded unrelated to the

Table 1
Definition of fever of unknown origin (FUO) and inflammation of unknown origin (IUO)\(^{[1-4]}\).

<table>
<thead>
<tr>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Fever (\geq 38.3^\circ C (\geq 101^\circ F)) for FUO OR</td>
</tr>
<tr>
<td>Elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or serum amyloid A (SAA) with body temperature (&lt; 38.3^\circ C (&lt; 101^\circ F)) for IUO</td>
</tr>
<tr>
<td>Duration of illness at least 3 weeks</td>
</tr>
<tr>
<td>No diagnosis despite extensive evaluation including (but not limited to):</td>
</tr>
<tr>
<td>Extensive medical history and physical examination</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) or serum amyloid A (SAA), hemoglobin, platelet count, leukocyte count including differentiation, sodium, potassium, calcium, creatinin, total serum protein en protein electrophoresis, alkaline phosphatase (AP), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), lactate dehydrogenase (LDH), creatinin kinase (CK), antinuclear antibodies (ANA), rheumatoid factor (RF), microscopic urinalysis, ferritin</td>
</tr>
<tr>
<td>Blood cultures (minimal 3), urine culture, tuberculin skin test or interferon gamma release assay</td>
</tr>
<tr>
<td>Chest x-ray, abdominal ultrasound, or chest and abdominal CT scan</td>
</tr>
<tr>
<td>Neutropenia (leukocyte count (&lt; 1.0 \times 10^9/L) or granulocyte count (&lt; 0.5 \times 10^9/L) during at least 1 week within the 3 months before the start of the fever</td>
</tr>
<tr>
<td>Known human immunodeficiency virus (HIV) infection</td>
</tr>
<tr>
<td>Known hypogammaglobulinemia (IgG &lt;50% of normal value)</td>
</tr>
<tr>
<td>Use of 10/mg prednisone or equivalent dose of corticosteroids during at least 2 weeks in the 3 months before the start of the fever</td>
</tr>
</tbody>
</table>

1. On several separate occasions:
   - Fever \(\geq 38.3^\circ C (\geq 101^\circ F)\) for FUO OR
   - Elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or serum amyloid A (SAA) with body temperature \(< 38.3^\circ C (< 101^\circ F)\) for IUO
   - Duration of illness at least 3 weeks
   - No diagnosis despite extensive evaluation including (but not limited to):
     - Extensive medical history and physical examination
     - Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) or serum amyloid A (SAA), hemoglobin, platelet count, leukocyte count including differentiation, sodium, potassium, calcium, creatinin, total serum protein en protein electrophoresis, alkaline phosphatase (AP), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), lactate dehydrogenase (LDH), creatinin kinase (CK), antinuclear antibodies (ANA), rheumatoid factor (RF), microscopic urinalysis, ferritin
     - Blood cultures (minimal 3), urine culture, tuberculin skin test or interferon gamma release assay
     - Chest x-ray, abdominal ultrasound, or chest and abdominal CT scan
   - Neutropenia (leukocyte count \(< 1.0 \times 10^9/L\) or granulocyte count \(< 0.5 \times 10^9/L\) during at least 1 week within the 3 months before the start of the fever
   - Known human immunodeficiency virus (HIV) infection
   - Known hypogammaglobulinemia (IgG <50% of normal value)
   - Use of 10/mg prednisone or equivalent dose of corticosteroids during at least 2 weeks in the 3 months before the start of the fever
underlying cause of the fever, after 38 and 42 months from presentation, respectively. (Table 4).

3.3. Prognosis during long-term follow-up

Ninety-nine of the 131 patients with unexplained FUO (75.6%) responded to the questionnaire for long-term follow-up. Median duration of follow-up in these patients was 75 months (range 28–177 months). (Table 2)

3.3.1. Treatment during long-term follow-up. Fifty-three of the 64 patients that received some form of treatment for unexplained FUO during the FUO study (82.8%) responded to the questionnaire. Twenty-eight of them (43.5%) reported that their fever had resolved. Median duration from the start of the fever to remission was 21 months (range 0–86 months).

Forty-six patients who remained untreated during the FUO study responded to the questionnaire and 20 of them (43.5%) reported spontaneous remission of fever. In untreated patients, median duration of fever was 2.0 months (range 0–45 months). This was not significantly different from treated patients (P = 0.19).

Ten of the 99 responders (10.1%) reported to have received some form of treatment for unexplained FUO that was not reported during the FUO studies (Table 3). In only 3 of them treatment was definitely started after the FUO study. One of these 3 reported to have been prescribed anakinra, the second used omalizumab and the third one reported to have been treated with nadropramine and acenocoumarol, all 3 in absence of an explanation.

Of all empirical treatments, 66.7% had been effective (Table 3).

3.3.2. Survival during long-term follow-up. Six patients (6.1%) died during long-term follow-up (Table 4). Median duration from first presentation to death was 13 months (range 3–24 months) and median age at death was 73 years (range 64–79 years). The cause of death was known in 4 patients and was considered unrelated to FUO in 3 of them. In 1 patient, who died from breast cancer, it was unclear whether the tumor could have been responsible for the febrile illness (Table 4).

3.3.3. Further investigation during long-term follow-up. Twenty-six of 99 responders (26.3%) reported to have visited another health-care provider because of FUO after the FUO study. These patients had visited a median of one health-care provider (range 1–3 providers).
Ten patients (10.1%) reported that a final diagnosis had been made after the FUO study (Table 5). Median duration from the first visit to the Radboudumc to the final diagnosis was 3 years (range 0.6–11 years). In 6 of the 10 patients that reported a diagnosis after the FUO study (60.0%), the diagnosis could not be confirmed after further investigation. Of all 6 unconﬁrmed diagnoses, 4 (66.7%) were considered unlikely to be related to FUO, 1 (16.7%) was considered possibly related to FUO, and 1 (16.7%) was considered a likely explanation for the FUO (Table 5).

4. Discussion

Of the 131 patients with FUO that remained unexplained in the 2 most recent Dutch FUO studies,10,11 9 died during a median follow up of 5 years. In untreated patients, spontaneous remission of fever was present in 47.3%.

Little is known on the prognosis of patients with unexplained FUO/IUO. Only a single study speciﬁcally designed to address prognosis in FUO has been performed until now.10 In this study 4 of 168 patients with unexplained FUO died during a follow up of at least 6 months, and in only 2 cases no diagnosis could be made upon autopsy. A previous and smaller Dutch FUO study has shown mortality rates of 4.0%.11 Other western-European studies showed mortality rates between 2.0% and 19.0% in unexplained FUO.3,5–8 The differences between these studies may arise from differences in patient selection, study design, and differences in health care systems. With a median follow up of 60 months, our study has the longest duration of follow up of all recent FUO studies.

In the 6 patients that died with a known cause of death, death was considered unrelated to the febrile disease in 5. All of these patients died from a frequently seen cardiac disease. In the sixth patient it remains unknown whether the breast cancer she died from could have been present at the time of FUO.

Spontaneous remission of FUO/IUO occurred in 47.3% of untreated patients. In other western-European studies this percentages varies between 15% and 88%,3,5–7,11–13 and in non-western European studies between 15% and 100%.14–19 The wide range of duration of fever shows that it may take a long time until fever resolves.

Empirical treatment was effective in 66.7% of patients, with a median duration of fever of 21 months. Based on the wide range of duration of fever, it could be debated whether the empirical treatment was truly effective, as it cannot be proven that the fever would have resolved spontaneously.

In 2 of the 3 patients reporting to have been treated for FUO after the FUO study, treatment with either anakinra or omalizumab was considered related to FUO, but was questionable in the third one, reporting having used acenocoumarol and nadroparine in absence of a diagnosis. Of these 3 patients, only in the patient that was started on omalizumab the reason for the start of this therapy was known: chronic urticaria in absence of a deﬁnite diagnosis.

It could be debated whether the empirical therapy initiated for unexplained FUO in the 2 recent Dutch FUO studies could have inﬂuenced the diagnostic yield in these studies. Of the 99 responders in this study, 26.3% reported to have visited another health care provider because of FUO after no explanation for FUO had been found in our FUO expertise center. This illustrates that the vast majority of patients with FUO/IUO is sufﬁciently reassured when no diagnosis can be found in an FUO expertise center. Ten out of the 99 patients in our study reported to have received a ﬁnal diagnosis for their FUO/IUO after the FUO study, but this diagnosis was considered not to be related to the FUO in half of them. Diagnoses with possible relation to FUO were recurrent aspiration, drug fever, Streptococcus viridans bacteraemia, thyroiditis, and familial Mediterranean fever. The diagnoses recurrent aspiration and S. viridans bacteraemia may have been masked by the use of antibiotics, but 1 of these 2 patients had not been treated with antibiotics during the FUO study. Of all 5 patients with an unlikely diagnosis, 1 patient had been diagnosed with Hodgkin lymphoma, and this patient had been treated with corticosteroids during the FUO study. However, the PET/CT that showed no signs of lymphoma during the FUO study, and the interval between presentation and
<table>
<thead>
<tr>
<th>Gender, age  (y)</th>
<th>Fever pattern</th>
<th>Diagnosis†</th>
<th>Diagnostic category</th>
<th>Treatment</th>
<th>Health care provider</th>
<th>Duration until diagnosis (mo)‡</th>
<th>Opinion on likelihood of relation to FUO†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 F, 50</td>
<td>Continuous</td>
<td>Aspiration pneumonia due to hiatus hernia (confirmed)</td>
<td>Infection</td>
<td>Fundoplication</td>
<td>Community hospital</td>
<td>135</td>
<td>Likely explanation for FUO. After analysis by a gastroenterologist, fundoplication because of hernia diaphragmatica was performed, after which the patient never had fever again. Confirmed by data received from the respective consultant.</td>
</tr>
<tr>
<td>2 F, 68</td>
<td>Recurrent</td>
<td>Drug fever on rosuvastatin (confirmed)</td>
<td>Miscellaneous</td>
<td>Stop rosuvastatin</td>
<td>General practitioner</td>
<td>12</td>
<td>Likely explanation for FUO. The patient reported she became fever free after stopping rosuvastatin, which she used during FUO evaluation. Confirmed by her primary physician.</td>
</tr>
<tr>
<td>3 F, 71</td>
<td>Recurrent</td>
<td>Recurrent S viridans bacteremia (confirmed)</td>
<td>Infection</td>
<td>Antibiotics, dental extraction</td>
<td>FUO expertise center</td>
<td>12</td>
<td>Likely explanation for the fever. Approximately 1 year after the FUO study, the patient had a fever episode with S viridans bacteria. PET/CT showed no contributory findings, but X-OPT showed lucent areas in the maxilla. After extraction of all teeth, the patient became afebrile.</td>
</tr>
<tr>
<td>4 F, 50</td>
<td>Recurrent</td>
<td>Ankylosing spondylitis (confirmed)</td>
<td>NID</td>
<td>None</td>
<td>Community hospital</td>
<td>136</td>
<td>Relationship unlikely due to long time-interval. Patient suffered from episodical back pain during FUO evaluation. PET/CT was normal. Diagnosis was confirmed by treating physician.</td>
</tr>
<tr>
<td>5 F, 47</td>
<td>Continuous</td>
<td>Thyroiditis and endometriosis (unconfirmed)</td>
<td>Other</td>
<td>Levothyroxin and uterus extirpation</td>
<td>Community hospital</td>
<td>6</td>
<td>Likely explanation for the fever. During FUO evaluation PET/CT showed increased FDG-uptake in the thyroid. Biopsy showed lymphocytic thyroiditis. Subclinical hypothyroditism was present. During the study, she did not report to have become fever free upon the start of levothyroxin, but now she is, and after stopping levothyroxin she reported to become febrile again. Approximately at the same time as the start of levothyroxin, uterus extirpation was performed.</td>
</tr>
<tr>
<td>6 M, 28</td>
<td>Recurrent</td>
<td>FMF (unconfirmed)</td>
<td>NID</td>
<td>Colchicine, anakinra</td>
<td>Hospital in other country</td>
<td>29</td>
<td>Possible explanation for the fever. This Turkish patient went to a consultant in Turkey, where amyloidosis was found in a skin biopsy. Mutation analysis for FMF was normal (2011) and the clinical picture is not fully consistent with FMF. He could also suffer from Behcet disease, as HLA-B51 is positive. Colchicine is not fully effective, but anakinra is.</td>
</tr>
<tr>
<td>7 M, 33</td>
<td>Recurrent</td>
<td>Pulmonary fungal infection (unconfirmed)</td>
<td>Infection</td>
<td>Antibiotics</td>
<td>Community hospital</td>
<td>53</td>
<td>Relation unlikely because of long time interval. Patient reported that a pulmonary fungal infection was diagnosed in a Dutch community hospital. He did not consent to the transferal of further data from this hospital to the study center. During FUO evaluation he had a cough. PET/CT showed 2 pulmonary non-FDG-positive nodules. No sputum cultures or other microbiological evaluations were performed.</td>
</tr>
<tr>
<td>8 M, 41</td>
<td>Recurrent</td>
<td>Hodgkin lymphoma (unconfirmed)</td>
<td>Malignancy</td>
<td>Chemotherapy</td>
<td>Community hospital</td>
<td>42</td>
<td>Relation unlikely because of long time interval. During FUO evaluation 2 chest CTs, 2 abdominal CTs, and a cerebral MRI showed no contributory findings. PET/CT before referral had shown slightly increased uptake in multiple lymph nodes and spleen, but 2 months later PET/CT in the Radboudumc was normal. Bone</td>
</tr>
</tbody>
</table>
Table 5 (continued)

<table>
<thead>
<tr>
<th>Gender, age (y)</th>
<th>Fever pattern</th>
<th>Diagnosis*</th>
<th>Opinion on likelihood of relation to FUO†</th>
<th>Treatment</th>
<th>Duration until diagnosis (mo)</th>
<th>Health care category</th>
<th>Diagnosis ‡</th>
<th>Opinion on likelihood of relation to FUO ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 F, 68</td>
<td>Recurrent</td>
<td>G-fever (unconfirmed)</td>
<td>Relationship unlikely.</td>
<td>None</td>
<td>24</td>
<td>Community hospital</td>
<td>Q-fever infection</td>
<td>Relationship unlikely. Q-fever serology IgM and IgG had been normal during FUO evaluation. We did not receive any data from the consultant who diagnosed this patient.</td>
</tr>
<tr>
<td>10 F, 63</td>
<td>Recurrent</td>
<td>Drug fever or NSALDs (unconfirmed)</td>
<td>Relationship unlikely.</td>
<td>Acetaminophen</td>
<td>49</td>
<td>Self diagnosis</td>
<td>Miscellaneous</td>
<td>Relationship unlikely. 66.7% of patients in the current study were treated with the interleukin-1 receptor antagonist anakinra. This drug is effective in autoinflammatory diseases. An increasing number of these are described in literature, but a significant proportion of patients with clear symptoms of autoinflammation cannot be diagnosed with one of the known autoinflammatory diseases, as these diseases are extremely rare and there are no investigations, besides genetic mutation analysis in some autoinflammatory diseases, that can definitely prove the presence of autoinflammation. After exclusion of other causes, anakinra could be tried in patients with symptoms of autoinflammation, such as fever, skin rash, and/or serositis. Anakinra has a rapid and substantial effect on fever and other symptoms. A rapid positive reaction to anakinra almost certainly proves the presence of autoinflammation, which is caused by overproduction of interleukin-1. The effectiveness of 66.7% found in this study illustrates that experts on this type of diseases are able to distinguish autoinflammation from other causes of FUO.</td>
</tr>
</tbody>
</table>

"Female, F = Familial Mediterranean fever, R/U = fever of unknown origin, M = male, NIID = non-infectious inflammatory disease, NSAIDs = non-steroidal anti-inflammatory drugs. From the first presentation of the patient at the treating physician, to the diagnosis of the febrile disease. From the first presentation of the patient at the treating physician, to the diagnosis of the febrile disease. Subjective opinion of the study team on the likeliness that the diagnosis was related to the episode(s) of FUO. Subjective opinion of the study team on the likeliness that the diagnosis was related to the episode(s) of FUO. From the first presentation of the patient at the treating physician, to the diagnosis of the febrile disease. From the first presentation of the patient at the treating physician, to the diagnosis of the febrile disease. Subjective opinion of the study team on the likeliness that the diagnosis was related to the episode(s) of FUO. Subjective opinion of the study team on the likeliness that the diagnosis was related to the episode(s) of FUO. From the first presentation of the patient at the treating physician, to the diagnosis of the febrile disease. From the first presentation of the patient at the treating physician, to the diagnosis of the febrile disease. Subjective opinion of the study team on the likeliness that the diagnosis was related to the episode(s) of FUO. Subjective opinion of the study team on the likeliness that the diagnosis was related to the episode(s) of FUO."
Author contributions
CM designed the study, collected data, analyzed the data, and drafted first and following version of manuscript. CE collected data. AS, JWMM, and CPB designed the study, supported data collection, and treated the patients. All authors approved the final version of the manuscript.

Conceptualization: Catharina M. Mulders-Manders, Anna Simon, and Chantal P. Bleeker-Rovers.

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Formal analysis: Catharina M. Mulders-Manders.

Resources: Chantal P. Bleeker-Rovers, Anna Simon and Jos WM van der Meer.

Supervision: Chantal P. Bleeker-Rovers and Anna Simon.

Writing – original draft: Catharina M. Mulders-Manders, Celeste Engwerda.

Writing – review and editing: Catharina M. Mulders-Manders, Anna Simon, Jos W.M. van der Meer, Chantal P. Bleeker-Rovers.

References