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Early VEGF testing in inflammatory neuropathy avoids POEMS syndrome misdiagnosis and associated costs

Short title: VEGF testing in POEMS syndrome

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Conflict of interest

No competing interests.

ABSTRACT

Background

Prompt diagnosis and early treatment prevents disability in POEMS syndrome. Delay in diagnosis is common with 55% of patients initially incorrectly diagnosed with Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). Patients are often treated with Intravenous Immunoglobulin (IVIG) which is both expensive and ineffective in the treatment of POEMS. Testing patients with acquired demyelinating neuropathy with serum vascular endothelial growth factor (VEGF) more accurately identifies POEMS syndrome than the current standard of care (SOC). Incorporating VEGF testing into screening could prevent misdiagnosis and reduce costs.

Methods

We used observed treatment information for patients in the University College London Hospital's (UCLH) POEMS syndrome database (n=100) and from the National Immunoglobulin Database to estimate costs associated with incorrect CIDP diagnoses across our cohort. We conducted a model-based cost-effectiveness analysis to compare the current diagnostic algorithm with an alternative which includes VEGF testing for all patients with an acquired demyelinating neuropathy.

Results

Treatment associated with an incorrect CIDP diagnosis led to total wasted healthcare expenditures of between £808,550 and £1,111,756 across our cohort, with an average cost-per-POEMS-patient misdiagnosed of £14,701 to £20,214. Introducing mandatory VEGF testing for patients with acquired demyelinating neuropathy would lead to annual cost-savings of £107,000 for the NHS and could prevent misdiagnosis in 16 cases per annum.

Conclusions

Misdiagnosis in POEMS syndrome results in diagnostic delay, disease progression and significant healthcare costs. Introducing mandatory VEGF testing for patients with acquired demyelinating neuropathy is a cost-effective strategy allowing for early POEMS diagnosis and potentially enabling prompt disease-directed therapy.

INTRODUCTION

Polyneuropathy Organomegaly Endocrinopathy Monoclonal-protein (M-protein) and Skin Changes (POEMS) syndrome is a rare but treatable cause of acquired peripheral neuropathy. Patients present with length dependent sensorimotor neuropathy, with mixed axonal and demyelinating features on neurophysiology.[1–4] Fifty-five percent of patients with confirmed POEMS are initially misdiagnosed as having Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), and are treated with immunomodulatory therapies including steroids, intravenous immunoglobulin (IVIG) and plasma exchange (PLEX).[5] IVIG is ineffective and costly (approximately £42.50 per gram in 2020), [6] often requires day case or hospital inpatient stays and can result in minor or severe complications. Diagnostic complexity results in a median time to POEMS diagnosis of 14 months, by which time over 30% of patients require a wheelchair or are bedbound.[5]

POEMS syndrome diagnosis relies on identification of a lambda light chain restricted paraprotein in combination with the typical neuropathy as hallmarks of disease.[7] Routine investigations to discover a monoclonal protein involve a serum protein electrophoresis (SPEP) and immunofixation. We have demonstrated in our UK cohort of 100 patients that the SPEP was positive in 55% of cases, and immunofixation in 78%.[5] It is common practice for laboratories to perform immunofixation only if a paraprotein is present on SPEP, despite studies indicating the superiority sensitivity of immunofixation in detecting low level monoclonal bands missed by conventional electrophoresis techniques.[8,9] Although modern high resolution electrophoresis can be as sensitive as immunofixation,[10] it is not in widespread use and has not been tested in POEMS syndrome cases which classically manifest small but significantly relevant monoclonal gammopathies. The data from our clinical cohort demonstrates a critical low level monoclonal band would not have been detected in 23% of cases by SPEP methodology only. The disparity

in SPEP and immunofixation techniques across laboratories, combined with differences in levels of sensitivity results in such tests often being difficult to interpret and rely upon.

Serum vascular endothelial growth factor (VEGF) of >1000pg/ml has high sensitivity (100%) and specificity (93%) in the diagnosis of POEMS syndrome, particularly when a demyelinating neuropathy and lambda light chain paraprotein present together. Levels are often very high (median pre-treatment VEGF levels in our cohort was 3594pg/ml), [5] and although iron deficiency anaemia, infection or chronic hypoxic states raise VEGF,[11–16] very high levels found with a demyelinating neuropathy and lambda light chain are diagnostic. This room temperature stable serum test can be sent to specialist labs for measurement, costing approximately £50 per sample.[17] We argue that an immunofixation and VEGF should be part of routine testing for patients presenting with an acquired peripheral neuropathy and with slowd conduction velocities on nerve conduction studies, particularly in those with suspected CIDP.

This study aims to add to the evidence base supporting a change in the polyneuropathy diagnostic process to include VEGF, uniquely from a cost-perspective. In particular, the study will estimate:

I. The cost of misdiagnosing POEMS syndrome patients with CIDP; and
II. The incremental cost-effectiveness ratio of a new POEMS diagnostic pathway.

METHODS

Our sequential cohort (n=100) was taken from the POEMS syndrome database of University College London Hospital's (UCLH), which includes clinical, diagnostic and treatment data. We collected additional data on IVIG treatment from the National Demand Management Programme for Immunoglobulin database. [18]

Costing analysis

The costing analysis focused on comparing the cost of patients directly diagnosed with POEMS syndrome, compared with patients diagnosed with POEMS subsequent to an incorrect CIDP diagnosis. For each activity leading up to a confirmed POEMS syndrome diagnosis (Figure 1), we estimated the quantity of resources used and multiplied these by their respective unit costs. A list of all costing inputs used is included in Supplementary Material I which presents all inputs and assumptions in this analysis.

As detailed IVIG treatment data, including number of treatments and IVIG quantity prescribed was only available for a sub-set of patients (n=26), we used information from the National Immunoglobulin Database to estimate the average cost of IVIG treatment-per-patient, and combined this with unit costs of plasma exchange and corticosteroids to estimate the total costs associated with an incorrect CIDP diagnosis for each patient. By multiplying average cost-per-POEMS syndrome patient misdiagnosed with CIDP by the number of misdiagnosed patients, we estimated the total cost associated with CIDP misdiagnoses across our cohort, following NICE guidelines that is the costs of the excess activities indicated in the pink shaded box in Figure 1.

Cost-effectiveness analysis

We used decision analytical modelling to compare the cost-effectiveness of the current diagnostic algorithm when investigating a patient with acquired demyelinating neuropathy (standard of care, SOC) with an alternative diagnostic algorithm which includes VEGF testing and mandatory immunofixation as follows, and detailed in figure 1:

1. Current Standard of care (SOC): SPEP; if positive, immunofixation
2. Intervention: SPEP, and immunofixation. VEGF testing in electrophysiologically confirmed acquired demyelinating polyneuropathy.

We modelled an incidence cohort of 3,635 patients with an inflammatory polyneuropathy as the study population, which we estimated to approximate the annual number of patients referred by a GP to neuromuscular clinics with any inflammatory polyneuropathy in the UK. [16] This estimate was based on the demographically similar population and healthcare system of the Netherlands as the nearest to the UK (Supplementary Materials IV). Patients transitioned through the decision tree according to test accuracy, misdiagnosis and treatment rates (Supplementary Material II). We used a time horizon from presentation with polyneuropathy symptoms, until a confirmed, correct diagnosis. POEMS syndrome diagnosis is typically between six months and two years, no discounting was applied. Input data and sources are described in Supplementary Material III.

Our model estimated the cost associated with each diagnostic pathway, and number of POEMS syndrome patients with a correct initial diagnosis. To evaluate cost-effectiveness using the incremental cost-effectiveness ratio (ICER); i.e. the added cost per additional correct POEMS syndrome diagnosis. We carried out one-way deterministic sensitivity analyses (DSA) and probabilistic sensitivity analysis (PSA), as detailed in the Supplementary Material III.

ETHICS

This study was approved by the London School of Hygiene and Tropical Medicine Ethics Committee. The retrospective cohort data of which this project became a part, was approved by the Health Research Authority and London Queen Square Research Ethics Committee.

RESULTS

Fifty-five patients of 100 (55%) were initially diagnosed as having CIDP, and eight patients were initially diagnosed with other diseases (5= Guillain-Barre syndrome, 1=Monoclonal gammopathy, 1= Vitamin B12 deficiency, 2= scleroderma). Median waiting time for a CIDP-misdiagnosed patient was 14 months (IQR: 7–24), compared to nine months (IQR 6 – 13) for patients directly diagnosed with POEMS syndrome; there was no significant difference in symptoms on diagnosis, or clinical outcomes between groups (Supplementary Material V).

Cost of CIDP misdiagnosis

Patients received between one and 10 treatments of IVIG (median 3, IQR: 1-5), and a median of 180 grams-per-treatment (IQR: 146–347g). The median Ig-cost per patient was £7,650 (IQR: £6,216-£14,769) and delivery cost, £12,795 (IQR: £4,265–£21,325). The median total IVIG treatment cost per patient with a CIDP misdiagnosis was £20,984 (IQR: £11,809– £30,349).

If we assume patients misdiagnosed with CIDP (n=55) with missing treatment information (n=15) received no treatment, the total costs of CIDP misdiagnosis across our cohort is £808,550 (average cost £14,701). However, if we assume these patients received treatment in the same proportions as the cohort for which treatment information is known (n=40) the total costs of CIDP misdiagnoses is £1,111,756 with a median cost of £20,214 per patient (IQR: 11,808 –30,348).[1]

[1] Calculated by multiplying recorded IVIG treatment data (grams per course, number of IVIG courses) by unit costs (Supplement I) for each patient, and summing all estimates (£676,2431) and dividing by n (=26)

Table 1: Costing and cost-effectiveness results

Costing analysis									
	Patients with CIDP misdiagnosis	**IVIG**		**Steroids**		**Plasma Exchange**		**Cost**	
Cohort	***n***	***n***	***Cost, £***	***n***	***Cost, £***	***n***	***Cost, £***	***Total, £***	***Av, £***
Conservative – assuming patients with no treatment info (n=15) received no treatment	55	38	797,383[1]	19	289[2]	6	10,879[3]	808,550	14,701
Extrapolated – assuming patients with missing treatment information received treatment in the same proportions as the cohort for which treatment is known	55	52[4]	1,096,401[1]	26	397[2]	8	14,958[3]	1,111,756	20,214
Cost-effectiveness analysis									
	Correct diagnoses	**Total cost, GBP** *(incorrect treatment costs, IFIX + VEGF screening costs)*							
Standard of care	12.5	£2,813,462 *(£213,107, £98,007)*							
Intervention	28.1	£2,706,064 *(£26,334, £179,584)*							
Incremental effect and costs	15.6	-£107,398							

Incremental cost effectiveness ratio	Dominates (£6,880 ***saved*** for each correct diagnosis)

1. Calculated by multiplying patients receiving IVIG [n] by median IVG treatment cost (£20,214)
2. Calculated by multiplying patients receiving treatment [n] by cost per course (£1,813.12; Supplement I)
3. Calculated by multiplying patients receiving treatment [n] by cost per course (£15.20; Supplement I)
4. ((38 (patients recorded to receive IVIG)/ 40 (patients with treatment information)) x 55

Cost-effectiveness analysis

The intervention diagnostic algorithm, in which all patients with acquired demyelinating polyneuropathy were screened with VEGF (including SPEP and immunofixation), would save £107,398 and result in 15.6 additional POEMS syndrome patients directly diagnosed per year across the UK (Table 1). The sensitivity analysis shows that the intervention dominated the SoC across uncertainty values (Supplementary Material VI).

DISCUSSION

Our study found that from a cohort of 100 POEMS syndrome patients, 55 were initially diagnosed with CIDP. Treatment associated with an initial incorrect CIDP diagnosis led to large, wasted healthcare expenditure. Treatment with IVIG alone was estimated to cost £20,984 per POEMS syndrome patient incorrectly diagnosed with CIDP, and we estimated that between 69% and 95% of misdiagnosed patients received IVIG treatment. When combined with the PLEX and corticosteroid treatment costs for patients recorded to have received these, the total wasted healthcare expenditure of CIDP misdiagnoses across our 100-patient cohort was between £808,550 - £1,111,756. This is a substantial waste of resources, and given the NHS is extremely resource constrained, carries a large opportunity cost. Incorrect IVIG treatment for POEMS patients may also have resulted in unnecessary harmful side effects. Indirect costs, such as time

lost at employment or education, travel costs for treatment, and the emotional and social impacts of diagnostic uncertainty were not evaluated in this study and thus the true cost to misdiagnosis is likely to be far higher than that calculated here.

Our cost-effectiveness analysis suggests misdiagnosis and associated costs could be reduced or avoided by a change in the diagnostic protocol. Introducing mandatory immunofixation with a SPEP for patients presenting with an inflammatory polyneuropathy, and VEGF testing for patients with an acquired demyelinating polyneuropathy (most often considered to represent CIDP) could immediately lead to annual cost-savings of £107,398 for the NHS. This pathway would require an increase in the number of VEGF and immunofixation tests but would result in a higher number of POEMS syndrome patients initially correctly diagnosed and therefore reduced waste expenditure for the treatment of incorrect conditions.

RECOMMENDATIONS

Routine inflammatory neuropathy screening with SPEP only is not adequately sensitive to detect small plasma cell clones. Monoclonal gammopathies that are correctly identified are additionally at risk of misinterpretation as a paraproteinaemic neuropathy or coincidental Monoclonal Gammopathy of Unknown Significance (MGUS) and thus IVIG treatment remains indicated. This study highlights the clinical and economic rationale firstly to test immunofixation in combination with SPEP in all cases presenting with inflammatory neuropathy. This is the most sensitive measure to identify relevant monoclonal gammopathies which may be associated with the neuropathy and require specific treatment. Once neurophysiology is performed, all cases of acquired demyelinating peripheral neuropathy (in which most are considered to be CIDP in the outpatients setting), particularly those where IVIG is being considered should receive a VEGF test (see figure 1). A significantly raised VEGF at this stage would be a strong indication of POEMS

syndrome and thus should prompt thorough exploration for an underlying monoclonal plasma cell disorder if not already discovered upon initial serological testing. Mildly elevated VEGF can occur rarely in other inflammatory neuropathies and haematological malignancies,[11] and therefore the combination of demyelinating neuropathy, significantly raised VEGF, and lambda paraprotein is essential to make a definitive POEMS diagnosis. Patients in our retrospective cohort diagnosed in less than six months from symptom onset had significantly lower ONLS scores (n=4) compared to those diagnosed after six months (n=6) ($p<0.05$) suggesting delayed diagnosis increases neuropathy severity.[5] Implementation of VEGF testing into routine clinical practice should correctly identify more POEMS cases from CIDP on initial presentation and avoid ineffective immunomodulatory therapy. Early diagnosis will allow for initiation of POEMS directed therapy resulting in improved patient outcomes. The ultimate objective of this newly proposed management strategy is to improve patients' quality of life, and ability to live and work independently.

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Short title: VEGF testing in POEMS syndrome

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ABSTRACT

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Prompt diagnosis and early treatment prevents disability in POEMS syndrome. Delay in diagnosis is common with 55% of patients initially incorrectly diagnosed with Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). Patients are often treated with Intravenous Immunoglobulin (IVIG) which is both expensive and ineffective in the treatment of POEMS. Testing patients with acquired demyelinating neuropathy with serum vascular endothelial growth factor (VEGF) more accurately identifies POEMS syndrome than the current standard of care (SOC). Incorporating VEGF testing into screening could prevent misdiagnosis and reduce costs.

Methods

We used observed treatment information for patients in the University College London Hospital's (UCLH) POEMS syndrome database (n=100) and from the National Immunoglobulin Database to estimate costs associated with incorrect CIDP diagnoses across our cohort. We conducted a model-based cost-effectiveness analysis to compare the current diagnostic algorithm with an alternative which includes VEGF testing for all patients with an acquired demyelinating neuropathy.

Results

Treatment associated with an incorrect CIDP diagnosis led to total wasted healthcare expenditures of between £808,550 and £1,111,756 across our cohort, with an average cost-per-POEMS-patient misdiagnosed of £14,701 to £20,214. Introducing mandatory VEGF testing for patients with acquired demyelinating neuropathy would lead to annual cost-savings of £107,000 for the NHS and could prevent misdiagnosis in 16 cases per annum.

Conclusions

Misdiagnosis in POEMS syndrome results in diagnostic delay, disease progression and significant healthcare costs. Introducing mandatory VEGF testing for patients with acquired demyelinaitng neuropathy is a cost-effective strategy allowing for early POEMS diagnosis and potentially enabling prompt disease-directed therapy.

BACKGROUND: Prompt diagnosis and early treatment prevents disability POEMS syndrome. Delay in diagnosis is common with 55% of patients incorrectly diagnosed with Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). Patients are often treated with Intravenous Immunoglobulin (IVIG) which is expensive and more importantly ineffective in the treatment of POEMS. Testing patients with acquired demyelinating neuropathy with serum vascular endothelial growth factor (VEGF) more accurately distinguishes POEMS from CIDP than the current standard of care (SOC). Incorporating VEGF testing into screening could prevent misdiagnosis and reduce costs.

METHODOLOGY: We used observed treatment information for patients in the University College London Hospital's (UCLH) POEMS syndrome database (n=100) and from the National Immunoglobulin Database to estimate costs associated with incorrect CIDP diagnoses across our cohort. We conducted a model-based cost-effectiveness analysis to compare the current diagnostic algorithm with an alternative which includes VEGF testing for patients with suspected CIDP.

RESULTS: Treatment associated with an incorrect CIDP diagnosis led to total wasted healthcare expenditures of between £808,550 and £1,111,756 across our cohort, with an average cost-per-POEMS-patient misdiagnosed of £14,701 to £20,214. Introducing mandatory VEGF testing for

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INTRODUCTION

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This study aims to add to the evidence base supporting a change in the polyneuropathy diagnostic process to include VEGF, uniquely from a cost-perspective. In particular, the study will estimate:

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II. The incremental cost-effectiveness ratio of a new POEMS diagnostic pathway.

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Cost-effectiveness analysis

We used decision analytical modelling to compare the cost-effectiveness of the current diagnostic algorithm when investigating a patient with acquired demyelinating neuropathy (standard of care, SOC) with an alternative diagnostic algorithm which includes VEGF testing and mandatory immunofixation as follows, and detailed in figure 1:

1. Current Standard of care (SOC): SPEP; if positive, immunofixation
2. Intervention: SPEP, and immunofixation. VEGF testing in electrophysiologically confirmed acquired demyelinating polyneuropathy.

We modelled an incidence cohort of 3,635 patients with an inflammatory polyneuropathy as the study population, which we estimated to approximate the annual number of patients referred by a GP to neuromuscular clinics with any inflammatory polyneuropathy in the UK. [16] This estimate was based on the demographically similar population and healthcare system of the Netherlands as the nearest to the UK ~~We modelled a cohort of 4,039 patients as the study population which we estimated to approximate the annual number of patients referred by a GP to neuromuscular clinics with an inflammatory polyneuropathy in the UK~~ (Supplementary Materials IV). Patients transitioned through the decision tree according to test accuracy, misdiagnosis and treatment rates (Supplementary Material II). We used a time horizon from presentation with polyneuropathy symptoms, until a confirmed, correct diagnosis. POEMS syndrome diagnosis is typically between six months and two years, no discounting was applied. Input data and sources are described in Supplementary Material III.

Our model estimated the cost associated with each diagnostic pathway, and number of POEMS syndrome patients with a correct initial diagnosis. To evaluate cost-effectiveness using the incremental cost-effectiveness ratio (ICER); i.e. the added cost per additional correct POEMS syndrome diagnosis. We carried out one-way deterministic sensitivity analyses (DSA) and probabilistic sensitivity analysis (PSA), as detailed in the Supplementary Material III.

ETHICS

This study was approved by the London School of Hygiene and Tropical Medicine Ethics Committee. The retrospective cohort data of which this project became a part, was approved by the Health Research Authority and London Queen Square Research Ethics Committee.

RESULTS

Fifty-five patients of 100 (55%) were initially diagnosed as having CIDP, and eight patients were initially diagnosed with other diseases (5= Guillain-Barre syndrome, 1=Monoclonal gammopathy, 1= Vitamin B12 deficiency, 2= scleroderma). Median waiting time for a CIDP-misdiagnosed patient was 14 months (IQR: 7–24), compared to nine months (IQR 6 – 13) for patients directly diagnosed with POEMS syndrome; there was no significant difference in symptoms on diagnosis, or clinical outcomes between groups (Supplementary Material V).

Cost of CIDP misdiagnosis

Patients received between one and 10 treatments of IVIG (median 3, IQR: 1-5), and a median of 180 grams-per-treatment (IQR: 146–347g). The median Ig-cost per patient was £7,650 (IQR: £6,216-£14,769) and delivery cost, £12,795 (IQR: £4,265–£21,325). The median total IVIG treatment cost per patient with a CIDP misdiagnosis was £20,984 (IQR: £11,809– £30,349).

If we assume patients misdiagnosed with CIDP (n=55) with missing treatment information (n=15) received no treatment, the total costs of CIDP misdiagnosis across our cohort is £808,550 (average cost £14,701). However, if we assume these patients received treatment in the same

proportions as the cohort for which treatment information is known (n=40) the total costs of CIDP misdiagnoses is £1,111,756 with a median cost of £20,214 per patient (IQR: 11,808 –30,348).[1]

Table 1: Costing and cost-effectiveness results

Costing analysis									
	Patients with CIDP misdiagnosis	**IVIG**		**Steroids**		**Plasma Exchange**		**Cost**	
Cohort	***n***	***n***	***Cost, £***	***n***	***Cost, £***	***n***	***Cost, £***	***Total, £***	***Av, £***
Conservative – assuming patients with no treatment info (n=15) received no treatment	55	38	797,383[1]	19	289[2]	6	10,879[3]	808,550	14,701
Extrapolated – assuming patients with missing treatment information received treatment in the same proportions as the cohort for which treatment is known	55	52[4]	1,096,401[1]	26	397[2]	8	14,958[3]	1,111,756	20,214

[1] Calculated by multiplying recorded IVIG treatment data (grams per course, number of IVIG courses) by unit costs (Supplement I) for each patient, and summing all estimates (£676,2431) and dividing by n (=26)

Cost-effectiveness analysis		
	Correct diagnoses	**Total cost, GBP** *(incorrect treatment costs, IFIX + VEGF screening costs)*
Standard of care	12.59.3	£3,030,6822,813,462 *(£213,107158,566, £105,80198,007)*
Intervention	20.928.1	£2,978,066706,064 *(£19,59526,334, £193,796179,584)*
Incremental effect and costs	11.615.6	-£52,616107,398
Incremental cost effectiveness ratio	Dominates (£4,5306,880 ***saved*** for each correct diagnosis)	

1. Calculated by multiplying patients receiving IVIG [n] by median IVG treatment cost (£20,214)
2. Calculated by multiplying patients receiving treatment [n] by cost per course (£1,813.12; Supplement I)
3. Calculated by multiplying patients receiving treatment [n] by cost per course (£15.20; Supplement I)
4. ((38 (patients recorded to receive IVIG)/ 40 (patients with treatment information)) x 55

Commented [EM1]: 20.9

Commented [EM2]: 11.6

Cost-effectiveness analysis

The intervention diagnostic algorithm, in which all patients with ~~suspected CIDP~~acquired demyelinating polyneuropathy were screened with VEGF (including SPEP and immunofixation), would save £52,616107,398 and result in 11.615.6 additional POEMS syndrome patients directly diagnosed per year across the UK (Table 1). The sensitivity analysis shows that the intervention dominated the SoC across uncertainty values (Supplementary Material VIVI).

DISCUSSION

Our study found that from a cohort of 100 POEMS syndrome patients, 55 were initially diagnosed with CIDP. Treatment associated with an initial incorrect CIDP diagnosis led to large, wasted

healthcare expenditure. Treatment with IVIG alone was estimated to cost £20,984 per POEMS syndrome patient incorrectly diagnosed with CIDP, and we estimated that between 69% and 95% of misdiagnosed patients received IVIG treatment. When combined with the PLEX and corticosteroid treatment costs for patients recorded to have received these, the total wasted healthcare expenditure of CIDP misdiagnoses across our 100-patient cohort was between £808,550 - £1,111,756. This is a substantial waste of resources, and given the NHS is extremely resource constrained, carries a large opportunity cost. Incorrect IVIG treatment for POEMS patients may also have resulted in unnecessary harmful side effects. Indirect costs, such as time lost at employment or education, travel costs for treatment, and the emotional and social impacts of diagnostic uncertainty were not evaluated in this study and thus the true cost to misdiagnosis is likely to be far higher than that calculated here.

Our cost-effectiveness analysis suggests misdiagnosis and associated costs could be reduced or avoided by a change in the ~~inflammatory polyneuropathy~~ diagnostic protocol. Introducing mandatory immunofixation with a SPEP ~~and VEGF into the screening tests~~ for patients presenting with an inflammatory polyneuropathy, and VEGF testing for patients with an acquired demyelinating polyneuropathy (most often ~~suspected~~considered to represent CIDP) ~~with an acquired demyelinating polyneuropathy~~ could immediately lead to annual cost-savings of £~~52,615~~107,398 for the NHS. This pathway would require an increase in the number of VEGF and immunofixation tests~~,~~ but would result in a higher number of POEMS syndrome patients initially correctly diagnosed and therefore ~~less~~ reduced waste expenditure ~~wasted~~ for the~~on~~ treatment ~~for~~ of incorrect conditions~~misdiagnoses~~.

RECOMMENDATIONS

Routine inflammatory neuropathy screening with SPEP only is not adequately sensitive to detect small plasma cell clones. Monoclonal gammopathies that are correctly identified are additionally at risk of misinterpretation as a paraproteinaemic neuropathy or coincidental Monoclonal Gammopathy of Unknown Significance (MGUS) and thus IVIG treatment remains indicated. This study highlights the clinical and economic rationale ~~to use~~ firstly to test immunofixation in combination with SPEP in all cases presenting with inflammatory neuropathy. This is the most sensitive measure to identify relevant monoclonal gammopathies which may be associated with the neuropathy and require specific treatment. Once neurophysiology is performed, all cases of ~~early VEGF testing in all patients presenting with an~~ acquired demyelinating peripheral neuropathy (in which most are considered to be CIDP in the outpatients setting), particularly those where IVIG is being considered should receive a VEGF test (see figure 1). A significantly raised VEGF at this stage would be a strong indication of POEMS syndrome and thus should prompt thorough exploration for an underlying monoclonal plasma cell disorder if not already discovered upon initial serological testing. Mildly elevated VEGF can occur rarely in other inflammatory neuropathies and haematological malignancies,[11] and therefore the combination of demyelinating neuropathy, significantly raised VEGF, and lambda paraprotein is essential to make a definitive POEMS diagnosis. ~~compared to standard routine screening,~~ Patients in our retrospective cohort diagnosed in less than six months from symptom onset had significantly lower ONLS scores (n=4) compared to those diagnosed after six months (n=6) ($p<0.05$) suggesting delayed diagnosis increases neuropathy severity.[5] ~~We believe that i~~implementation of VEGF testing into routine clinical practice~~, for which sensitive identification of a lambda light chain associated paraprotein with immunofixation is essential for interpretation, would~~ should correctly identify more POEMS cases from CIDP on initial presentation and~~,~~ avoid~~ing~~ ineffective immunomodulatory therapy. Early diagnosis will allow for ~~and more quickly instigate~~initiation of POEMS directed therapy resulting in improved patient outcomes. The ultimate objective of this

newly proposed management strategy is to improve patients' quality of life, and ability to live and work independently.

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SUPPLEMENTARY MATERIAL

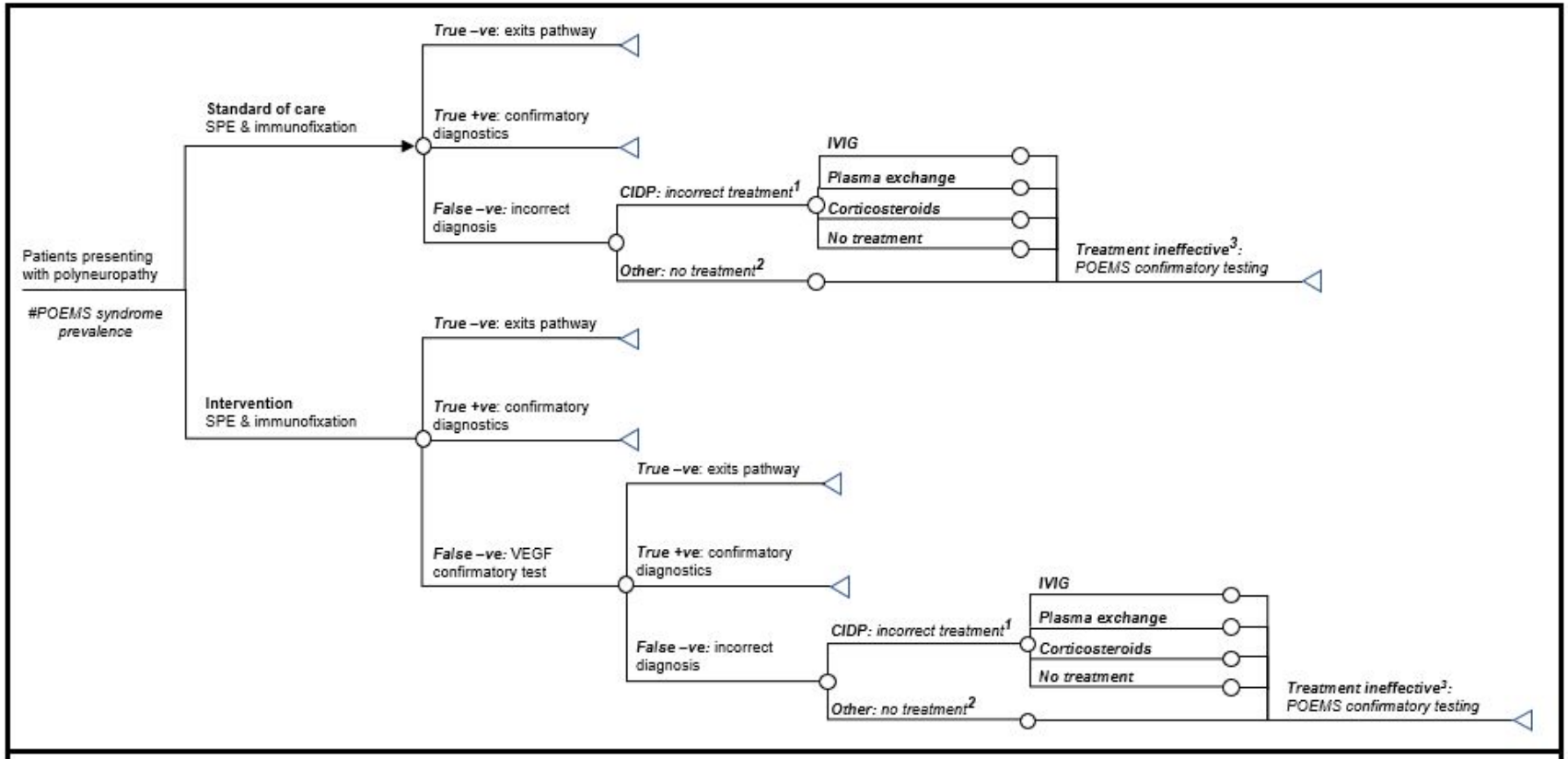
I. IVIG costing inputs

	Unit cost (GBP)	Quantity	Cost per course (GBP)
IVIG			
Medication cost	42.50[1]	*Derived*	*Derived*
Delivery costs (personnel and services)	853.00	5	4,265.00
Plasma Exchange			
Drug cost	52.53[2]	21[3]	1,103.12
Delivery cost (personnel and services)	142.00	5	710.00
Corticosteroids			
Drug cost[4]	3.80[5]	4	15.20

1. Cost per kg
2. Octaplas, cost per 200ml
3. 5 treatments of 12ml per kg, 70kg person (4.2 units)
4. Prednisolone (20mg daily for 4 months); alternatively, patients might be prescribed a course of Dexamethasone (6 months @ 4 x 40mg tablets). This treatment has been found to have similar outcomes to prednisolone but is much more expensive, and therefore likely used infrequently.
5. Cost per month

Note: All sources included in Supplementary Materials III

II. Decision-tree model structure



1. Decision tree shows simplification for illustration. On CIDP diagnosis, patients may receive IVIg, plasma exchange, corticosteroids, any combination of these, or no treatment. Therefore, these probabilities intentionally do not add up to 1.
2. In reality, patients wrongly diagnosed with a non-CIDP diagnosis will likely receive some treatment before their diagnosis is reconsidered. However, these treatments have been excluded as they represent only a small proportion of incorrect treatments.
3. This model assumes that all treatment for CIDP will be ineffective for POEMS syndrome patients, and after the prescribed treatment course, patients' symptoms will be re-evaluated, POEMS syndrome suspected, and confirmatory tests conducted.

III. Costing inputs and model parameter estimates

Parameter	Mean base case	SE	DSA[1] lower – upper	PSA[2] Distribution (α, β)	Source
Prevalence estimates					
CIDP, as % of patients with inflammatory polyneuropathy	7.2%	0.05*	2 - 10	Beta (4,32)	Calculated (see IV)
POEMS syndrome, as % of patients with inflammatory polyneuropathy	0.8%	0.003*	0.25 - 3.00	Beta (4, 718)	*Calculated (see IV)*
Diagnostic test sensitivity					
SPE	55%	0.05	45 – 65	Beta (54, 45)	Keddie et al. [2]
Immunofixation	78%	0.04	69 – 85	Beta (77, 22)	Keddie et al. [2]
VEGF	94%	0.03	87 – 98	Beta (82, 5)	Keddie et al. [2]
Misdiagnosis rates (on false negative test result)					
CIDP	87%	0.04	76 – 94	Beta (54, 8)	*Estimated from UCLH cohort*
Other	13%	0.04	-	Beta (8, 54)	*Estimated from UCLH cohort*
Treatment for CIDP misdiagnosis (conservative estimate: assuming patients with no treatment info (n=15) received no treatment)					
IVIG	69%	0.06	55 – 80	Beta (37, 17)	*Estimated from UCLH cohort*
Plasma exchange	11%	0.04	-	Beta (6, 48)	*Estimated from UCLH cohort*
Corticosteroids	35%	0.06	-	Beta (19, 35)	*Estimated from UCLH cohort*
No treatment	27%	0.06	-	Beta (15, 39)	*Estimated from UCLH cohort*
Costs					
POEMS diagnosis					
Procedures					
Blood sample	£3.00	-	-	Deterministic	NHS Reference costs [3]
Nerve conduction/ electromyography	£189.00	-	-	Deterministic	NHS Reference costs [3]
Bone marrow biopsy	£177.00	-	-	Deterministic	NHS Reference costs [3]
Bone lesion	£275.84	-	-	Deterministic	NHS Reference costs [3]
PET scan	£470.71	-	-	Deterministic	NHS Reference costs [3]
Tests (test, reagent and personnel costs)					
SPEP	£16.80	-	-	Deterministic	Personal comms [4]
Immunofixation	£44.80	-	-	Deterministic	Personal comms [4]
VEGF	£55.00	-	-	Deterministic	UCLH Neuroimmunology Handbook [5]
Bone marrow biopsy processing	£290.00	-	-	Deterministic	Personal comms [6]
Consultations					
GP appointment	£37.00	-	-	Deterministic	2018 Unit Costs of Health and Social Care [7]
Consultant-led first clinic appointment	£211.00	-	-	Deterministic	NHS Reference costs [3]
Consultant-led follow-up clinic appointment	£221.00	-	-	Deterministic	NHS Reference costs [3]

Treatment for CIDP misdiagnosis					
Drug costs					
IVIG cost per gram	£42.50	-	£14.17 - £127.50	Deterministic	2016 NHS Policy Document [8]
PE (Octaplas, cost per 200ml)	£220.63	-	-	Deterministic	Open Prescribing database [9]
Prednisolone (20mg, 30 tablets)	£3.80	-	-	Deterministic	Open Prescribing database [9]
Treatment variables					
IVIG days per course	5	2.5*	2 – 7[2]	Gamma (4, 1)	Gorson et al. 2012 [10]
Number of treatments for per course of PE	1	0.5*	2 – 7[2]	Gamma (4, 1)	Gorson et al. 2012 [10]
Number of courses of PE	5	2.5*	1 – 4[2]	Gamma (4, 0)	Gorson et al. 2012 [10]
Hospital charges					
Outpatient admission for IVIG	£853.00	-	-	Deterministic	NHS Reference costs [3]
Outpatient admission for PE	£142.00	-	-	Deterministic	NHS Reference costs [3]

1. Deterministic Sensitivity Analysis
2. Probabilistic Sensitivity Analysis

IV. Prevalence estimates

We used CIDP and POEMS syndrome prevalence among patients presenting with an inflammatory polyneuropathy, rather than national estimates, to match the starting cohort of the decision-tree. We obtained an estimate of the proportion of polyneuropathy cases presenting to a hospital with an inflammatory polyneuropathy [1]], polyneuropathy and CIDP incidence rates, and CIDP and POEMS prevalence rates [11] from the literature. We divided CIDP incidence by our calculated inflammatory polyneuropathy incidence to estimate the proportion of inflammatory polyneuropathy patients with CIDP and used the prevalence rate ratio of CIDP to POEMS to approximate the proportion of inflammatory polyneuropathy patients with POEMS syndrome in our base-case.

	Per 100,000	Incident cases	%
National polyneuropathy incidence	77 [1]	40,391[1]	
Inflammatory polyneuropathy incidence (% of polyneuropathy)		3,635[2]	9.0 [1]
National CIDP incidence	0.5 [11]	262[1]	
National CIDP prevalence	2.8 [11]		
National POEMS syndrome prevalence	0.3 [11]	28[1]	
CIDP prevalence among patients presenting with an inflammatory polyneuropathy			7.2[3]
POEMS prevalence among patients presenting with an inflammatory polyneuropathy			0.8[4]

1. Case calculated by multiplying incidence rate multiplied by UK adult population
2. Calculation: national polyneuropathy incidence * % polyneuropathy cases that are inflammatory
3. Calculation: CIDP incidence (262)/ National inflammatory polyneuropathy incidence (3,635)/ *100
4. Calculation: CIDP as % of inflammatory polyneuropathy (7.2%)* prevalence rate ratio POEMS (0.3): CIDP (2.8)

V. Cohort demographics and outcome analysis

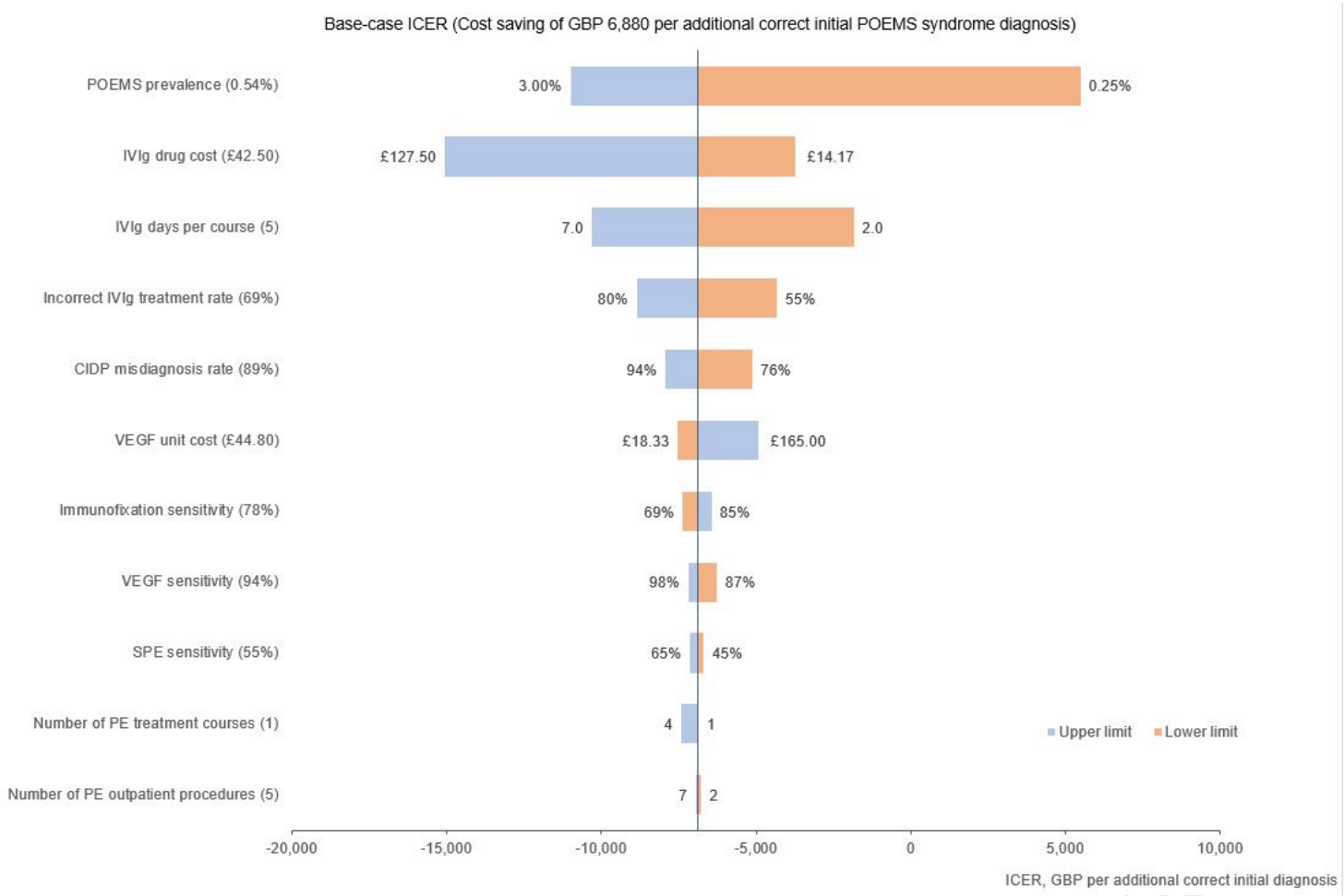
Variable	N	All (95% CI/ IQR)[1]	Direct (95% CI/ IQR)	Indirect - CIDP (95% CI/ IQR)	Indirect -other (95% CI / IQR)	p value
Descriptive statistics						
Cohort size (%)	100	-	37 (28 – 47)	55 (45 – 65)	8.0 (4.0 – 15)	-
Males (%)	69	69 (60 – 78)	65 (48 – 79)	71 (57 – 81)	75 (37 -94)	-
Age at diagnosis (mean)	100	55 (52 – 57)	55 (50 – 61)	53 (50 – 57)	59 (45 – 73)	0.78[2]
Waiting time						
Symptoms to diagnosis, months (median)	100	11 (7.0 – 21)	9.0 (6.0 – 13)	14 (7.0 – 24)	8.0 (6.1 – 13)	0.11[3]
Pre-diagnosis						
Total no of symptoms (mean)	100	7 (3.0 – 12)	7.1 (6.4 – 7.7)	7.1 (6.6 – 7.5)	6.5 (5.0 – 8.0)	0.67[2]
Mobility score (median)	99	3.6 (3.0 – 5.0)	3.0 (1.5 – 5)	4.0 (3.0 – 5.0)	3.5 (3.0 – 5.0)	0.38[3]
Wheelchair/ bedbound (%)	99	37 (28 – 48)	36 (20 – 53)	38 (25 – 51)	18 (0.0 – 81)	0.98[4]
ONLS (median)	100	6 (4.0 – 8.0)	5.0 (3.0 – 8.0)	7.0 (4.0 – 9.0)	6.5 (4.0 – 8.5)	0.13[3]
Post-diagnosis						
Mobility score (median)	99	1.5 (1.0 – 3.5)	1.5 (1.0 – 3.5)	3.0 (2.0 – 4.0)	3.0 (1.5 – 3.0)	0.10[3]
Wheelchair/ bedbound (%)	99	12 (6.4 - 20)	8.3 (0.0 – 17)	16 (6.3 – 26)	0 (0 – 0)	0.26[3]
ONLS[5] (median)	52	4.0 (3.0 – 5.0)	3.5 (1.5 – 5.5)	4.0 (2.0 – 5.0)	4.0 (4.0 – 5.0)	0.84[3]
Clinical response (%)	56	65 (52 – 77)	54 (33 – 76)	69 (52 – 86)	100 (100 – 100)	0.26[4]
Haematological response (%)	89	48 (38 – 59)	53 (35 – 71)	47 (32 – 61)	33 (0 .0 – 88)	0.64[4]
VEGF response (%)	90	79 (69 – 87)	71 (54 – 87)	82 (70 – 93)	100 (100 – 100)	0.24[4]
Relapse (%)	100	32 (23 - 42)	32 (17 – 48)	35 (22 – 48)	13 (0.0 – 42)	0.40[4]
Mortality (%)	100	12 (6.3 – 20)	13 (2.0 – 25)	13 (3.6 – 22)	0 (0.0 – 0.0)	0.91[4]

Abbreviations: CI=Confidence Interval; IQR=Interquartile Range

1. 95% CI shown for means or proportions, IQR shown for median values
2. ANOVA test statistic
3. Kruskal-Wallis H test statistic
4. Likelihood Ratio (LR) Chi-Square test
5. ONLS measured 3 years after treatment completion

VI. Cost-effectiveness analysis

Figure 1: Deterministic sensitivity analyses of Incremental Cost-Effectiveness Ratios (ICERs) for Intervention vs Current Standard of Care.



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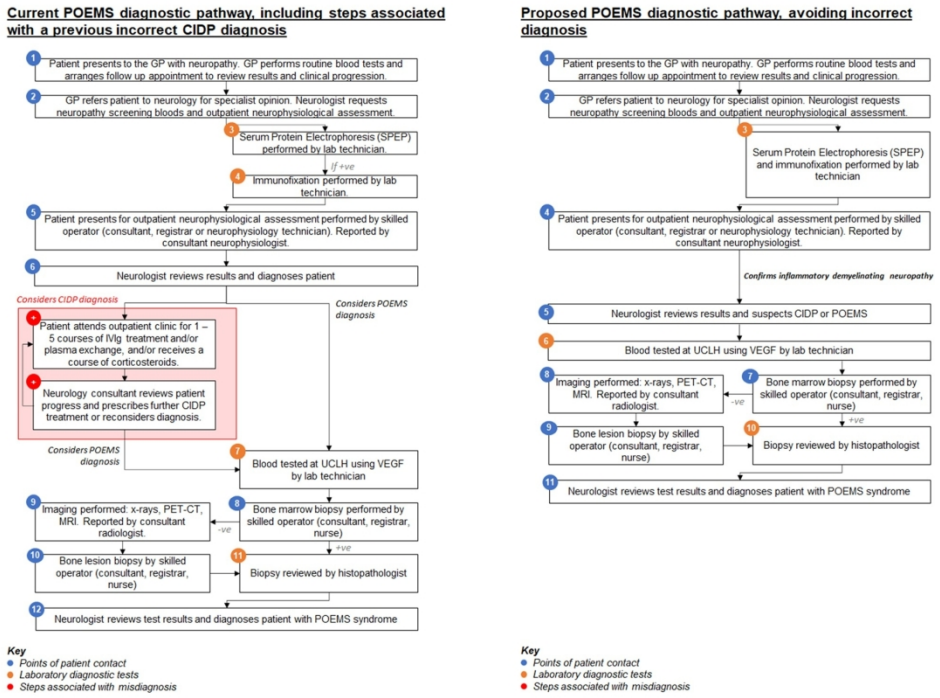

Figure 1: Current POEMS syndrome diagnostic pathway (left) compared to proposed POEMS diagnostic pathway, avoiding incorrect diagnosis

560x393mm (96 x 96 DPI)