Diagnostic pathways in multiple myeloma and their relationship to end organ damage: an analysis from the Tackling Early Morbidity and Mortality in Myeloma (TEAMM) trial

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Frequency of doses: 12-24, until the bleeding is resolved. *Moderate haemorrhage:* More extensive haemarthrosis, muscle bleeding, haematoma. Factor VIII level required (IU/dL or % of normal): 30-60. Frequency of doses: 12-24, until the bleeding is resolved. *Severe or life-threatening haemorrhages:* Factor VIII level required (IU/dL or % of normal) – 60-100. Frequency of doses: 8-24, until the threat is resolved Perioperative management: *Minor surgery Including tooth extraction.* Factor VIII level required (IU/dL or % of normal): 30-60. Frequency of doses (hours): within one hour before surgery; repeat after 24 hours if necessary. Duration of therapy: single dose or repeat injection every 24 hours for at least 1 day until healing is achieved. *Major surgery.* Factor VIII level required (IU/dL or % of normal): 80-100 (pre- and post-operative). Frequency of doses (hours): Within one hour before surgery to achieve factor VIII activity within the target range. Repeat every 8 to 24 hours to maintain factor VIII activity within the target range. Repeat injection every 8 to 24 hours as necessary until adequate wound healing is achieved. Consider continuing therapy for another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL). Prophylaxis: The recommended dose is 50 IU of Esperoct per kg body weight every 4 days. Adjustments of doses and administration intervals may be considered based on achieved factor VIII levels and individual bleeding tendency. Paediatric population: The dose in adolescents (12 years and above) is the same as for adults. In children below 12 years long-term safety has not been established. 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ABR, annualised bleed rate; EHL, extended half-life; FVIII, factor VIII; rFVIII, recombinant factor VIII; SHL, standard half-life

[†]Previously treated patients, 12 years and above.[1] [††] Prophylaxis: The recommended dose is 50 IU of Esperoct per kg body weight every 4 days. Adjustments of doses and administration intervals may be considered based on achieved factor VIII levels and individual bleeding tendency.[1] [§]Total ABR includes all bleeds: spontaneous, traumatic and joint bleeds[4]

References: 1. Esperoct® Summary of Product Characteristics. **2.** Adynovi® Summary of Product Characteristics. **3.** Elocta® Summary of Product Characteristics. **4.** Giangrande P et al. Thromb Haemost 2017; 117:252–261. **5.** Tiede A et al. J Thromb Haemost 2013; 11:670–678. **6.** Advate® Summary of Product Characteristics. **7.** NovoEight® Summary of Product Characteristics. **8.** Nuwiq® Summary of Product Characteristics. **9.** Refacto AF® Summary of Product Characteristics.

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bjh research paper

Diagnostic pathways in multiple myeloma and their relationship to end organ damage: an analysis from the Tackling Early Morbidity and Mortality in Myeloma (TEAMM) trial

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Summary

Multiple myeloma is associated with significant early morbidity and mortality, with considerable end organ damage often present at diagnosis. The Tackling EArly Morbidity and Mortality in Multiple Myeloma (TEAMM) trial was used to evaluate routes to diagnosis in patients with myeloma and the relationship between diagnostic pathways, time to diagnosis and disease severity. A total of 915 participants were included in the study. Fifty-one per cent were diagnosed by direct referral from primary care to haematology; 29% were diagnosed via acute services and 20% were referred via other secondary care specialties. Patients diagnosed via other secondary care specialties had a longer diagnostic interval (median 120 days vs. 59 days) without an increase in features of severe disease, suggesting they had a relatively indolent disease. Marked intrahospital delay suggests possible scope for improvement. A quarter of those diagnosed through acute services reported >30 days from initial hospital consultation to haematology assessment. Participants diagnosed through acute services had poorer performance status ($P < 0{\cdot}0001$) and higher burden of end organ damage ($P < 0{\cdot}0001$) with no difference in the overall length of diagnostic pathway compared to those diagnosed by direct referral (median 59 days). This suggests that advanced disease in patients presenting through acute services predominantly reflects disease aggression.

Keywords: multiple myeloma, diagnostic pathways, diagnostic delay, primary care, time to diagnosis.

Multiple myeloma is a plasma cell malignancy, with an annual incidence of 5,600 cases and 3,000 deaths in the UK.[1,2] Patients often have poor performance status at diagnosis. This can be due to end organ damage associated with the disease, including hypercalcaemia, infection, renal impairment or failure, anaemia and bone disease.[3-5] Myeloma is commonly diagnosed in older age, (median age at diagnosis of 70 years),[6]where comorbidities are common. Chronic kidney disease unrelated to myeloma can be seen in 25% of patients[7,8] and cardiovascular disease, diabetes and cerebrovascular disease are frequently present.[9,10] There is significant early mortality after diagnosis, often related to

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infection, renal failure and cardiovascular events, with 10% of patients dying within 60 days of starting anti-myeloma treatment.[4] Despite recent advances in myeloma treatment with the use of novel therapies, death from infection remains high during the first year.[11]

Early diagnosis is recognised as important in improving cancer outcomes nationally.[12,13] Previous research shows that patients with myeloma have a prolonged pathway to diagnosis. Howell *et al*. showed a median time from first consultation to diagnosis of 163 days [interquartile rang (IQR) 84–306], suggesting many patients have a protracted diagnostic pathway.[14] Delays occur in both the patient interval, from first symptom onset to first healthcare consultation, and in the diagnostic interval from first healthcare consultation to final diagnosis.[15-17] Previous research suggests those who experience a longer pathway before myeloma diagnosis are more likely to have late stage disease at diagnosis.[16,18]

Although many patients are diagnosed following referral from primary care, in the UK 34% of patients present as an emergency, for example through presentation to Emergency Medicine in secondary care hospitals. These patients have high mortality in the first year after diagnosis, with a 12-month net survival of 61·7% vs. 87·5% in those diagnosed by referral from primary care to haematology services.[19] Because of the non-specific nature of the presenting symptoms, which include back pain, bone pain and lethargy, there is also potential for patients to be referred from primary care to secondary care specialist services other than haematology if myeloma is not initially suspected.[18,20] How these pathways relate to delays in diagnosis, particularly in those seeing other secondary care specialties before referral to haematology, has not been fully explored previously.

The Tackling EArly Morbidity and Mortality in Multiple Myeloma (TEAMM) trial was a supportive care trial and included a planned assessment of the diagnostic pathways of patients with multiple myeloma in the UK, and the association between route to diagnosis and disease severity.

Methods

The TEAMM trial was a double-blind, placebo-controlled trial of supportive care, with a primary focus of investigating levofloxacin prophylaxis for 12 weeks to reduce infection in patients newly diagnosed with myeloma.[21] This study was conducted at 93 hospitals within the UK (Table S1).

Ethical approval was provided by NHS Research Ethics Committee West Midlands, Coventry and Warwickshire. Sponsorship was provided by the University of Birmingham and University of Warwick.

Eligible patients were recruited between 15 August 2012 and 29 April 29th 2016 (Table S2). Data were collected at initial trial recruitment regarding pathway to diagnosis, with analysis of this data planned *a priori*. This included age, gender, ethnicity, performance status at diagnosis and 6 months prior (using the Eastern Cooperative Oncology Group performance status scale),[22] radiological evidence of bone disease and blood test results at diagnosis, including full blood count, calcium level, creatinine and estimated glomerular filtration rate. Components of the International Staging System (ISS) score were documented, allowing calculation of disease stage.[23]

End organ damage was assessed through the presence of hypercalcaemia, renal impairment, anaemia and bone disease (CRAB features) using the International Myeloma Working Group (IMWG) criteria for myeloma diagnosis (Table S3).[24] Survival at 12 months was recorded. Supplementary questions were included at recruitment regarding consultation with healthcare services and symptoms prior to diagnosis. The first question was '*With hindsight, what were the first symptoms that we can now attribute to myeloma and when did they occur?*'. After the first 197 participants this was amended to '*When did the patient first notice bodily changes and/or symptoms that they attribute to the myeloma?*' to ensure agreement with the newly published Aarhus statement.[25] The question included four lines to record the symptoms, plus date of onset for each line.

The other questions asked were as follows:

1. When did the patient first visit a doctor or nurse at their local general practice about any of these symptoms or bodily changes?
2. How many times did the patient consult a doctor or nurse at their local general practice about any of these symptoms or bodily changes before they were referred (or diagnosed, if no GP referral)?
3. When did the patient first visit the hospital [includes accident and emergency (A&E)]?
4. Which hospital department was the patient first seen in (includes A&E)?
5. When did the patient first see a haematologist about any of these symptoms?

Responses were used to categorise the diagnostic pathway, based on the first hospital department where the patient was seen, and to measure intervals within the diagnostic pathway.

For the purposes of this study, three pathways were assessed: (i) diagnosis subsequent to attendance in acute services, (ii) direct referral from primary care to haematology, (iii) referral to haematology via other secondary care specialty (Fig 1).

Those reporting consultation in the Emergency Department, or an acute medical or surgical admissions unit were classified as diagnosed after attending acute services, this included those with prior consultation within primary care, in keeping with definitions used by Public Health England.[26]

Those reporting haematology services as their first hospital contact were classified as direct referral to haematology. Those not diagnosed via the acute pathway or direct pathway were classified as diagnosed via the other secondary care pathway if sufficient information was available to determine which department reviewed the participant.

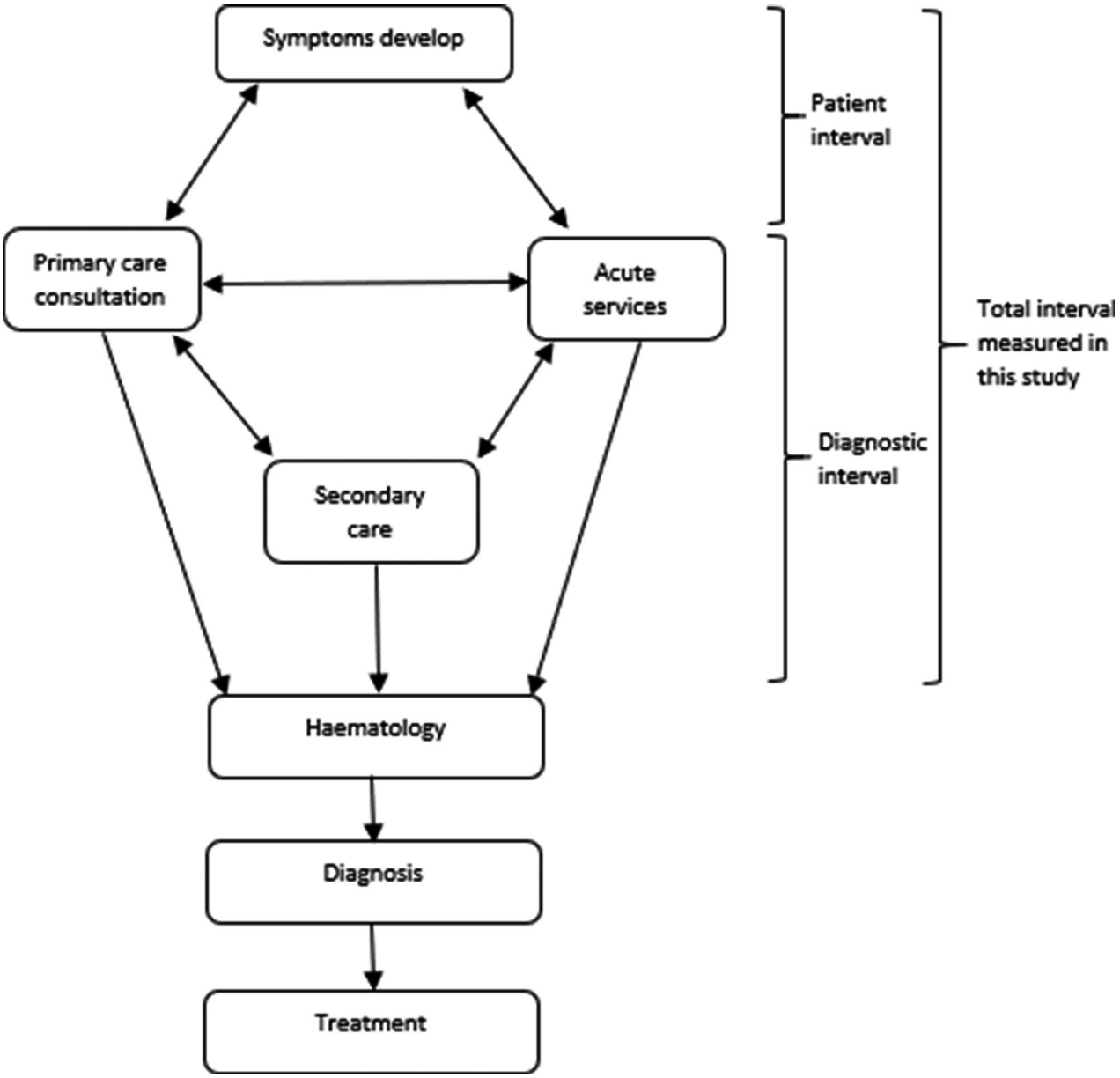

Fig 1. Possible pathway steps taken by patients during diagnostic pathway, from initial symptom onset to diagnosis and treatment. Intervals as measured in this study. Arrows show direction of travel & referral.

Intervals were chosen to align with recommendations from the Aarhus statement[25] and were determined from the dates provided (Fig 1). Patient intervals compare the date of earliest symptom onset and the date of earliest healthcare consultation (in primary or secondary care). Diagnostic intervals compare the date of first healthcare consultation and haematology consultation. As the date of diagnosis was not provided, the date of first haematology consultation was used as a surrogate marker. All dates were collected from patient recall.

Statistical analyses were performed using IBM SPSS statistics (IBM, Armonk, NY, USA). Mean and standard deviation are reported for normally distributed variables; median (IQR) are reported where variables are not normally distributed. All statistical tests are described in the text, figure or table legends. A P value of $<0{\cdot}05$ signifies statistical significance throughout.

Results

Participant characteristics

In total, 977 participants were recruited into the TEAMM trial. Diagnostic pathways were available for 915 participants;

the remaining participants had not recorded enough information to determine their diagnostic pathway and were excluded from the study.

Of these 915 participants, 468 (51%) were diagnosed by direct referral from primary care to haematology, 269 (29%) were diagnosed via acute services and 178 (20%) were referred via another secondary care specialty (Table 1). Table 2 shows the specialties assessing participants in the 'other secondary care' pathway. The most common specialties seeing these participants were trauma and orthopaedics, gastroenterology or gastrointestinal/colorectal surgery, respiratory medicine and renal medicine.

There was no significant difference in the age of participants presenting via each pathway (Kruskal-Wallis $P = 0{\cdot}052$). A higher proportion of those referred directly from primary care to haematology were female compared to those seen in acute services (chi square $P = 0{\cdot}016$). There was a higher proportion of participants from ethnic backgrounds other than white British in the acute pathway compared with the direct referral pathway (chi square $P = 0{\cdot}023$).

Diagnostic intervals

Overall, the median time from symptom onset to haematology review was 70 days (Table 1, Fig S1). Patients diagnosed via the 'direct' pathway had the same total interval as those diagnosed via the 'acute' pathway. Those diagnosed via the 'other secondary care' pathway had a significantly longer pathway than either the direct or acute pathways, with a median of 120 days from initial symptom onset to haematology review (Kruskal-Wallis $P < 0{\cdot}001$).

The median patient interval was 3 days (IQR 0–54) (Fig S2). There was no significant difference in the reported patient interval between the pathways (Kruskal-Wallis $P = 0{\cdot}065$).

The median diagnostic interval was 42 days (Fig. S3). Those diagnosed through 'other secondary care' services had a longer diagnostic interval than those diagnosed via the acute or direct pathways (Kruskal-Wallis $P < 0{\cdot}001$).

Intrahospital delay, from first secondary care consultation to haematology review, was assessed (Fig S4). Those diagnosed via 'other secondary care' services had a longer intrahospital delay than those diagnosed via the 'acute' pathway (Kruskal-Wallis $P < 0{\cdot}001$).

Primary care consultation in participants diagnosed through acute services

Of those diagnosed via acute services, 195 participants (72·5%) had been seen in primary care prior to, or the same day as, attending acute services. The median length of time from primary care consultation to acute services presentation was 18 days (IQR 0–78). Fifty participants (25·6%) were seen in primary care the same day that they attended acute services. There was no difference in age, gender or ethnicity comparing those who had seen primary care previously and those who had not (age, Mann-Whitney U $P = 0{\cdot}08$; gender, chi square $P = 0{\cdot}82$; ethnicity, chi square $P = 0{\cdot}34$).

Markers of severity and end organ damage

At diagnosis, 10·2% of patients did not have end organ damage as defined by IMWG criteria.

Comparing by diagnostic pathway, there was no significant difference in the proportion of patients with hypercalcaemia (chi square $P = 0{\cdot}18$). There was a higher rate of renal impairment in those presenting via acute or 'other secondary care' pathways compared with those presenting through the direct pathway (chi square $P < 0{\cdot}001$). There was also a higher rate of anaemia in the acute pathway participants compared with the direct pathway (chi square $P < 0{\cdot}001$), but no difference in those seen in 'other secondary care' compared to the other pathways. Bone disease was more common in those diagnosed via the acute pathway compared to the direct pathway or 'other secondary care' pathway (chi square $P < 0{\cdot}001$).

Table 1 shows the performance status, ISS and CRAB features reported per participant in each pathway. Patients presenting via acute pathways were more likely to have two or more CRAB features present at diagnosis (chi square $P < 0{\cdot}001$).

Those attending via acute pathways were more likely to have a worse ISS than those presenting via the direct pathway or 'other secondary care' pathway (chi square $P < 0{\cdot}001$). They were also more likely to have a performance status of grade 3 or 4 at diagnosis (chi square $P < 0{\cdot}001$). There was no difference in the reported performance status at 6 months prior to diagnosis between each pathway (chi square $P = 0{\cdot}66$). Those diagnosed via acute pathways were more likely to have a deterioration in performance status of more than one grade from 6 months prior to diagnosis to first haematology consultation (chi square $P < 0{\cdot}001$).

Survival

Twelve-month survival was 92% for those diagnosed via the direct pathway, 91% for those diagnosed through acute services and 86% for those diagnosed through 'other secondary care' services. There was no difference in overall survival at 12 months from diagnosis between the pathways (logrank $P = 0{\cdot}07$).

Discussion

This study represents the most comprehensive analysis of diagnostic pathways in multiple myeloma to date, providing unique data on pathways within secondary care and the relationship between end organ damage and diagnostic pathway intervals for each route to diagnosis.

Table 1. Comparison of participants seen via each diagnostic pathway.

		Overall (n = 915)		Direct pathway 51% of participants (n = 468)		Acute pathway 29% of participants (n = 269)		Other secondary care pathway 20% of participants (n = 178)		
		N	%	*N*	%	*N*	%	*N*	%	
Age (years)	Median	67		68		67		66		P = 0.052
	Under 40	10	1.1%	4	0.9%	3	1.1%	3	1.7%	
	40–49	59	6.4%	20	4.3%	24	8.9%	15	8.4%	
	50–59	157	17.2%	75	16.0%	49	18.2%	33	18.5%	
	60–69	329	36.0%	177	37.8%	86	32.0%	66	37.1%	
	70–79	255	27.9%	137	29.3%	73	27.1%	45	25.3%	
	80+	104	11.4%	55	11.8%	33	12.3%	16	9.0%	
Gender	Male	571	62.4%	271	57.9%	181	67.3%	119	66.9%	P = 0.016
Ethnicity	White British	803	87.8%	419	89.7%	224	83.2%	160	89.9%	P = 0.023
Diagnostic pathway intervals (measured in days)										
Total interval: 1st symptom to haematology review	Median (IQR)	70 (29–174) (N = 836)		59 (25–161) (N = 423)		59 (19–138) (N = 239)		120 (69–268) (N = 174)		P < 0.001
Patient interval: 1st symptom to first consultation	Median (IQR)	3 (0–54) (N = 732)		6 (0–59) (N = 352)		0 (0–37) (N = 239)		8 (0–71) (N = 141)		P = 0.065
Diagnostic interval: first consultation to haematology review	Median (IQR)	42 (15–113) (N = 803)		33 (13–88) (N = 384)		35 (8–100) (N = 265)		102 (47–181) (N = 155)		P < 0.001
Intra-hospital interval: 1st hospital visit to haematology review	Median (IQR)	N/A		N/A		9 (2–30) (N = 262)		30 (9–60) (N = 173)		P < 0.001
CRAB features										
		N	%	*N*	%	*N*	%	*N*	%	
Hypercalcaemia	Yes	42	5.8%	18	5.1%	19	8.1%	5	3.9%	P = 0.18
	No	676	94.2%	336	94.9%	216	91.9%	124	96.1%	
	Unknown	*197*		*114*		*34*		*49*		
Renal impairment	Yes	78	10.6%	18	4.9%	45	18.8%	15	11.4%	P < 0.001
	No	660	89.4%	349	95.1%	194	81.2%	117	88.6%	
	Unknown	*177*		*101*		*30*		*46*		
Anaemia	Yes	377	51.0%	159	43.4%	151	62.9%	67	50.4%	P < 0.001
	No	362	49.0%	207	56.6%	89	37.1%	66	49.6%	
	Unknown	*176*		*102*		*29*		*45*		
Bone disease	Yes	649	71.3%	311	66.6%	219	82.6%	119	66.9%	P < 0.001
	No	261	28.7%	156	33.4%	46	17.4%	59	33.1%	
	Unknown	*5*		*1*		*4*		*0*		
Markers of severity										
		N	%	*N*	%	*N*	%	*N*	%	
CRAB features present	0	71	10.0%	51	14.5%	7	3.1%	13	10.1%	P < 0.001
	1	355	50.0%	195	55.4%	88	38.4%	72	55.8%	
	≥2	284	40.0%	106	30.1%	134	58.5%	44	34.1%	
	Unknown	205		*116*		*40*		*49*		
ISS	1	206	26.6%	117	29.8%	42	19.0%	47	29.2%	P < 0.001
	2	341	44.0%	193	49.1%	87	39.4%	61	37.9%	
	3	228	29.4%	83	21.1%	92	41.6%	53	32.9%	
	Unknown	*140*		*75*		*48*		*17*		
ECOG performance status at randomisation	0–2	836	93.0%	439	96.3%	231	86.8%	166	93.8%	P < 0.001
	3–4	63	7.0%	17	3.7%	35	13.2%	11	6.2%	
	Unknown	*16*		*12*		*3*		*1*		

Table 1. (*Continued*)

		Overall (n = 915)		Direct pathway 51% of participants (n = 468)		Acute pathway 29% of participants (n = 269)		Other secondary care pathway 20% of participants (n = 178)		
		N	%	*N*	%	*N*	%	*N*	%	
ECOG performance status 6 months before randomisation	0–2	871	98.6%	441	98.9%	257	98.1%	173	98.9%	$P = 0.66$
	3–4	12	1.4%	5	1.1%	5	1.9%	2	1.1%	
	Unknown	*32*		*22*		*7*		*3*		
ECOG performance status deterioration of more than one grade	Yes	112	12.7%	30	6.7%	65	24.8%	17	9.7%	$P < 0.001$
	No	770	87.3%	415	93.3%	197	75.2%	158	90.3%	
	Unknown	*33*		*23*		*7*		*3*		

Data shown for the 915 participants where a diagnostic pathway could be determined. The intrahospital interval is not displayed here for total participants or direct pathway as this is not applicable to the direct pathway. Range for total interval was 0–3810 days for the direct pathway, 0–5777 days for the acute pathway and 0–5358 for the other secondary care pathway.
Gender: $P = 0{\cdot}016$ for direct pathway *versus* acute and other secondary care pathways; ethnicity: $P = 0{\cdot}023$ for proportion of patients who were not white British in acute pathway *versus* direct pathway. Renal impairment: $P < 0{\cdot}001$ for acute pathway *versus* direct pathway and for other secondary care *versus* direct pathway; anaemia: $P < 0{\cdot}001$ for acute *versus* direct pathway; bone disease: $P < 0{\cdot}001$ for acute *versus* direct pathway and acute *versus* other secondary care pathway. IQR, interquartile range.

In this large cohort, most patients were referred from their general practitioner directly to haematology, while 29% were diagnosed through acute services, and 20% were referred from their GP to a secondary care specialty other than haematology, seeing a wide range of medical and surgical specialties.

Those seen by acute services had poorer performance status, worse disease staging and more features of end organ damage at diagnosis, and higher rates of deterioration in performance status over the preceding 6 months. However, there was no difference in the total time interval, from symptom onset to diagnosis, in those diagnosed via acute services compared to those diagnosed via direct referral from primary care to haematology, or in the initial performance status 6 months prior to diagnosis. This suggests that poorer prognosis in patients diagnosed through acute services is not due to poorer baseline performance status in these patients. It may reflect aggressiveness of disease, rather than delays in the diagnostic process, as they develop a more advanced disease within the same timeframe.

Three quarters of patients diagnosed via the acute pathway had consulted primary care prior to assessment in acute services. Patients' symptoms may worsen following initial review necessitating emergency presentation, or patients with severe symptoms requiring urgent management may self-present to primary care but require immediate referral to acute services when severe illness is recognised. This does not equate to a failing primary care process, but to correct usage of the system, with primary care teams able to recognise and refer the most unwell patients to secondary care acute services.

Those referred to a non-haematology secondary care specialty had a significantly longer pathway to diagnosis, due to an increased diagnostic interval, between first consultation and haematology review. This is likely to reflect a doubled administrative and waiting time produced by referral to two specialties sequentially. Despite this longer pathway, patients had a similar performance status and ISS score to those referred directly to haematology, and fewer features of end organ damage than those diagnosed via acute services. This suggests patients diagnosed through this pathway may have relatively indolent disease, as a longer diagnostic course was not associated with more advanced disease. As the disease is less aggressive, it may have presented with less classic features and, therefore, have been more difficult to recognise as myeloma, explaining why these patients were referred to other specialties. Many of these other specialties are those expected to recognise and manage the complications of myeloma, for instance orthopaedics may identify those with bone disease, or renal medicine identify myeloma-related renal disease. This long pathway may, however, negatively impact patient experience.

Although differences in rates of end organ damage at diagnosis and prognostic features have been noted before in those diagnosed via different pathways,[20] this has not previously been compared to diagnostic pathway intervals for each route to diagnosis.

This study did have some limitations. The definition of acute diagnosis used here differed from that used in Routes to Diagnosis, as data were not available regarding urgency of outpatient referral. Subsequently, emergency outpatient referrals were not classified as acute diagnoses within TEAMM. In this cohort, 29% were diagnosed through acute services, compared to 34% nationally as described in Routes to Diagnosis.[26]

Table 2. Secondary care specialties where participants were seen in 'other secondary care' pathway.

Secondary care specialty	Number of participants	Percentage of those in other secondary care pathway (n = 178)	Percentage overall (n = 915)
Orthopaedics	35	19·7	3·8
Gastroenterology & GI surgery	29	16·3	3·2
Respiratory	21	11·8	2·3
Renal medicine	19	10·7	2·1
Oncology	16	9	1·7
Rheumatology	9	5·1	1
Urology	9	5·1	1
General medicine	8	4·5	0·9
Neurology & neurosurgery	7	3·9	0·8
Cardiology	6	3·4	0·7
ENT surgery	5	2·8	0·5
GI surgery	4	2·2	0·4
Geriatrics	3	1·7	0·3
Endocrinology	3	1·7	0·3
General surgery	3	1·7	0·3
Cardiothoracic surgery	1	0·6	0·1
Dermatology	1	0·6	0·1
Gynaecology	1	0·6	0·1
Ophthalmology	1	0·6	0·1
Pain clinic	1	0·6	0·1%

Table shows the number of participants reporting these speciality as first hospital department contact, the percentage of those in the 'other secondary care' pathway seeing this specialty (out of 178 participants), and the percentage of participants overall reporting seeing this specialty (of the 915 participants where pathway to diagnosis could be determined). ENT, Ear, Nose and Throat surgery; GI, gastrointestinal.

The diagnostic intervals described here are shorter than previously reported. The median time from symptom onset to haematology review was 70 days, which is shorter than the 156 days reported by Neal *et al.*[27] and the 163 days reported by Howell *et al.*[14] This may reflect the cohort of patients recruited to TEAMM, who were relatively young compared to those with myeloma overall, with a relatively good performance status.[6] This may reflect the TEAMM study protocol, which required participants to keep a patient diary, and collect nasal swabs and stool samples over 4 months. Patients who were more unwell may have found this too taxing. Also, those not planned for active treatment were excluded. If those with very long pathways were too unwell to participate, the length of the diagnostic pathway may have been underestimated. Similarly, patients who died before the diagnosis was confirmed or treatment initiated would not be included and, therefore we cannot comment on the diagnostic pathways taken by this subgroup of patients.

This shorter interval may also relate to the definition of date of diagnosis used here. Date of haematology consultation provided a surrogate for date of diagnosis, and although this is a recognised method of defining the date of diagnosis,[25] the date of histological diagnosis is likely to be later, leading to longer pathway intervals. In addition, diagnostic pathway intervals were based on patient recall, which is prone to time interval underestimation.[28] The pathway length reported here is, therefore, likely to be an underestimate. As all pathways were assessed using this method, and there is unlikely to be any effect of pathway on time from haematology consultation to histological diagnosis, comparisons between the pathways remain valid.

This study uses severity markers including staging, performance status and end organ damage to compare the diagnostic pathways. End organ damage may have been underestimated as this was based on results at trial recruitment, where hypercalcaemia, anaemia or severe acute kidney injury may have already been treated. There was no difference in survival at 12 months between the pathways in this study. As survival is known to vary by pathway to diagnosis, with poorer survival in those presenting through acute services,[20,26] this may again reflect that this cohort were comparatively well compared to the overall myeloma patient population, and those diagnosed through acute services with advanced organ damage causing severe symptoms may be less likely to be recruited into trials. These findings should be further explored in a wider cohort of patients diagnosed through acute services.

Although these findings did not suggest longer diagnostic pathways in those diagnosed via acute services, many of these patients still experienced delays before haematology review, with 25% reporting over 30 days from initial hospital attendance to haematology consultation. Further research is needed in this subgroup of patients to explore the causes of this delay and implement strategies for improvement, such as robust follow-up pathways of laboratory investigations.

Strategies to improve survival in those diagnosed through acute services focussed solely on reducing the length of the diagnostic pathway may have only limited effect. The diagnostic pathway is no longer in those diagnosed through acute services than in those diagnosed through direct referral to haematology from primary care; therefore, poorer prognosis in these patients is unlikely to be entirely attributable to delays in diagnosis. Diagnosis through acute services may be unavoidable for some with aggressive disease. This has significant implications for early diagnosis programmes, and strategies that are not reliant on early identification of symptoms need to be explored, such as targeted screening.

Conclusion

Delay in diagnosis remains a major problem in multiple myeloma. Patients are diagnosed through multiple pathways,

with route to diagnosis linked to aggressiveness of disease. Those diagnosed through acute services do not experience a longer diagnostic pathway but have a poorer performance status and higher burden of end organ damage, probably reflecting more aggressive disease.

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Conflicts of interest

SB reports honoraria from Celgene and Takeda and research funding from Takeda. KY reports honoraria and research funding from Amgen and Janssen. MTD reports Equity Ownership in Abingdon Health. The authors declare no conflicts of interest.

Authorship contributions

MTD, SB, JAD, TP, GI, GP, and KY originated the idea for the study and together with EL were responsible for the study design, conduct of the trial, data collection, analysis and write up. RDN advised on the supplementary questions and write up. CA was responsible for data analysis and write up. All authors read and approved the final manuscript.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Total interval by pathway to diagnosis. Cumulative histogram showing the time in days from first symptom onset to haematology review for patients seen via each pathway, for those with intervals up to 730 days.

Fig S2. Patient interval by pathway to diagnosis. Cumulative histogram showing the time in days from first symptom onset to haematology review for patients seen via each pathway, for those with intervals up to 365 days.

Fig S3. Diagnostic interval by pathway to diagnosis. Cumulative histogram showing the time in days from first symptom onset to haematology review for patients seen via each pathway, for those with intervals up to 365 days.

Fig S4. Intrahospital interval by pathway to diagnosis. Cumulative histogram showing the time in days from first symptom onset to haematology review for patients seen via each pathway, for those with intervals up to 365 days.

Table S1. Inclusion and exclusion criteria of the TEAMM trial.

Table S2. Features of end organ damage in multiple myeloma.

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