Journal of
Medical Genetics

Genetic testing in motor neurone disease and frontotemporal dementia: a five-year multicentre evaluation

Journal:	*Journal of Medical Genetics*
Manuscript ID	jmedgenet-2021-107776.R1
Article Type:	Short report
Date Submitted by the Author:	n/a
Complete List of Authors:	Cairns, Lauren; University Hospital Southampton NHS Foundation Trust Rankin, Julia; Royal Devon and Exeter NHS Trust, Clinical Genetics Hamad, Asma; Birmingham Women's and Children's NHS Foundation Trust, Clinical Genetics Unit Cooper, Nicola; Birmingham Women's and Children's NHS Foundation Trust, Clinical Genetics Unit Merrifield, Katrina; Birmingham Women's and Children's NHS Foundation Trust, Clinical Genetics Unit Jain, Vani; University Hospital Wales, All Wales Medical Genetics Service Rosser, Elisabeth; Great Ormond Street Hospital for Children NHS Foundation Trust, Clinical Genetics Unit Rogers, Megan; University Hospitals Bristol NHS Foundation Trust, Bristol Regional Clinical Genetics Service Buston, Sarah; University Hospitals Bristol NHS Foundation Trust, Bristol Regional Clinical Genetics Service Stopford, Cheryl; Leeds Teaching Hospitals NHS Trust, Yorkshire Regional Genetics Service Jones, Gabriela; Nottingham University Hospitals NHS Trust, Clinical Genetics Service Lefroy, Henrietta; Oxford University Hospitals NHS Foundation Trust, Oxford Centre for Genomic Medicine Nemeth, Andrea; John Radcliffe Hospital, University of Oxford, Nuffield Department of Clinical Neurosciences Holden, Simon; Cambridge University Hospitals NHS Foundation Trust, Department of Clinical Genetics Douglas, Andrew; University Hospital Southampton NHS Foundation Trust, Human Development and Health; University of Southampton, Human Development and Health
Keywords:	Motor neurone disease, Genetic Testing, Dementia, Neurodegenerative Diseases

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Genetic testing in motor neurone disease and frontotemporal dementia: a five-year multicentre evaluation

Authors:
Lauren M Cairns[1], Julia Rankin[2], Asma Hamad[3], Nicola Cooper[3], Katrina Merrifield[3], Vani Jain[4], Elisabeth Rosser[5], Megan Rogers[6], Sarah Buston[6], Cheryl Stopford[7], Gabriela Jones[8], Henrietta Lefroy[9], Andrea H Németh[9], Simon T Holden[10], Andrew G. L. Douglas[1, 11]

Author Affiliations:
1. Wessex Clinical Genetics Service, University Hospital Southampton NHS Foundation Trust, Southampton, UK
2. Peninsula Clinical Genetics, Royal Devon and Exeter Hospital, Exeter, UK
3. Clinical Genetics Unit, Birmingham Women's and Children's Hospital, Birmingham, UK
4. All Wales Medical Genetics Service, University Hospital Wales, Cardiff, Wales, UK
5. Clinical Genetics Department, Great Ormond Street Hospital, London, UK
6. Bristol Regional Genetics Service, St Michael's Hospital, Bristol, UK
7. Department of Clinical Genetics, Chapel Allerton Hospital, Leeds, UK
8. Clinical Genetics Service, Nottingham University Hospitals NHS Trust, Hucknall Road, Nottingham, UK
9. Oxford Centre for Genomic Medicine, Nuffield Orthopaedic Centre, Oxford, UK
10. Clinical Genetics, Addenbrooke's Treatment Centre, Cambridge, UK
11. Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK

Correspondence to:
Dr Andrew Douglas, Wessex Clinical Genetics Service, University Hospital Southampton NHS Foundation Trust, Southampton, UK
Tel: +44(0)23 8120 6170
E-mail: andrew.douglas@uhs.nhs.uk

Word count: 2000
(excluding title page, abstract, references, figures and tables)

ABSTRACT

Introduction: Motor neurone disease (MND) and frontotemporal dementia (FTD) comprise a neurodegenerative disease spectrum. Genetic testing and counselling is complex in MND/FTD owing to incomplete penetrance, variable phenotype and variants of uncertain significance. Affected patients and unaffected relatives are commonly referred to clinical genetics to consider genetic testing. However, no consensus exists regarding how such genetic testing should best be undertaken and on which patients.

Objective: We sought to ascertain UK clinical genetics testing practice in MND/FTD referrals, with the aim of helping inform guideline development.

Methods: MND/FTD clinical genetics referrals comprising both affected patients and unaffected relatives between 2012 and 2016 were identified and a standardised proforma used to collate data from clinical records.

Results: 301 referrals (70 affected, 231 unaffected) were reviewed across 10 genetics centres. Previously identified familial variants were known in 107 cases and 58% subsequently underwent testing (8/8 diagnostic and 54/99 predictive). Median number of genetic counselling appointments was two for diagnostic and four for predictive testing. Importantly, application of current UK Genomic Test Directory eligibility criteria would not have resulted in detection of all pathogenic variants observed in this cohort.

Conclusion: We propose pragmatic MND/FTD genetic testing guidelines based on appropriate genetic counselling.

KEYWORDS

Motor neurone disease; MND; amyotrophic lateral sclerosis; ALS; frontotemporal dementia; FTD; *C9orf72*; genetic testing

INTRODUCTION

Motor neurone disease (MND), also known as amyotrophic lateral sclerosis (ALS), is an incurable adult-onset neurodegenerative disorder with a worldwide incidence of 1.75/100,000.[1] Some 5% of MND appears familial, following autosomal dominant inheritance with variable penetrance, and pathogenic variants in over 30 different genes have been aetiologically implicated.[2, 3] The most commonly involved genes in familial MND are *C9orf72* ([MIM: 614260] a hexanucleotide GGGGCC expansion in up to 40%), *SOD1* ([MIM: 147450] pathogenic variants in 12%), *TARDBP* ([MIM: 605078] 4%) and *FUS* ([MIM: 137070] 4%), with other genes each accounting for 1% or less.[4] Up to 23% of MND patients also fulfil diagnostic criteria for frontotemporal dementia (FTD) and up to half of MND patients experience FTD-like symptoms and/or signs.[5, 6] FTD and MND constitute a disease spectrum and some 12.5% of FTD patients are also diagnosed with MND, while up to 40% experience MND-like symptoms and/or signs.[7] FTD has an overall incidence of 2.7-4.1/100,000 and at least 10% of cases display clear autosomal dominant inheritance, while up to 40% exhibit some family history.[8, 9] Pathogenic variants in at least 12 genes have been linked to FTD; the most frequent being the *C9orf72* hexanucleotide expansion, present in up to 25%, and variants in *GRN* (MIM: 138945) and *MAPT* (MIM: 157140), accounting for up to 15% and 6% of familial cases respectively.[10]

With growing availability of genetic testing, it has become apparent that no well-defined guidelines exist as to which patients are most suitable for testing and which genes to test on a clinical diagnostic basis. Practice therefore varies between centres across both clinical genetics and neurology specialities, depending on local expertise and interests. With the introduction of the UK Genomic Medicine Service, which seeks to standardise testing

provision across genetic disorders via its Test Directory, we sought to ascertain the MND/FTD genetic testing practice within UK clinical genetics services and guide the development of pragmatic genetic testing criteria.

METHODS

We conducted a service evaluation using a standardised proforma to collect data from patients referred to UK clinical genetics centres from 1st January 2012 to 31st December 2016. Ethics committee approval was not required for this evaluation. The dates chosen reflected a five-year period coinciding with introduction of genetic testing for the *C9orf72* expansion. Clinical records relating to MND/FTD referrals were reviewed for referral source, disease status, family history, presence of known familial mutation, genetic counselling, genetic testing and results, and subsequent clinical referrals. Positive family history was taken as presence of at least two affected first- or second-degree relatives.

RESULTS

Over the five-year period, 301 MND/FTD referrals with relevant data were received from across 10 UK clinical genetics centres: Wessex, Exeter, Birmingham, Wales, London (North East Thames), Bristol, Leeds, Nottingham, Oxford and Cambridge. General practice was the most common referral source (63%, 191/301), followed by neurology (24%, 71/301) and psychiatry (7%, 20/301). Details of referral source, disease status, familial variants, tests performed and appointment data are shown in figure 1, while overall patient numbers and outcomes for this evaluation are shown in figure 2.

Affected patients comprised 23% of referrals (70/301). Of these, 35 had FTD (50%), 32 had MND (46%) and three had both diagnoses (4%). The majority of affected patients (67%,

47/70) also had a family history of MND/FTD. Of these individuals, eight (17%) already had a pathogenic variant known in their family. All eight subsequently underwent genetic testing and all were found to carry a pathogenic variant (seven cases of *C9orf72* expansions and one *SOD1* variant). Interestingly, of the 39 remaining affected individuals with a family history but no previously known familial variant, 11 (28%) did not undergo genetic testing, while pathogenic variants were subsequently identified in 46% (13/28) of individuals who did have testing. These comprised 11 *C9orf72* expansions and two *SOD1* variants. One third of affected patients (23/70) had no family history of MND/FTD and no known familial pathogenic variant. Of these affected individuals, seven (30%) did not have genetic testing. Diagnostic testing was undertaken in the other 16 and a pathogenic *C9orf72* expansion was identified in four cases (25%).

Unaffected relatives of affected individuals comprised 77% of referrals (231/301). Of these, 99 (43%) had a previously known pathogenic variant in the family. Just over half of these individuals (55%, 54/99) chose to undergo predictive genetic testing while 45% (45/99) did not. Out of 54 unaffected relatives who had predictive testing, a pathogenic variant was identified in 25 (46%): 23 *C9orf72* expansions (including two of intermediate size), one *SOD1* variant and one *MAPT* variant. Notably, in the absence of a known familial pathogenic variant for which to predictively test, no unaffected relatives underwent blind genetic testing, irrespective of whether or not there was a positive family history of two or more affected individuals. Interestingly, 51% of unaffected relative referrals (117/231) only had one affected relative in the family, although 40 of these (34%) had a known familial pathogenic variant.

Overall, 36% (107/301) of referred patients had a pathogenic variant already known in their family. This was most commonly the *C9orf72* expansion (76%, 81/107), while *SOD1* comprised 6% (6/107) and *MAPT* and *GRN* each comprised 5% (5/107). Additional familial pathogenic variants in this cohort were in *TARDBP* (three variants), *FUS* and *VCP* ([MIM: 601023] one variant each). *C9orf72* was the most frequently requested diagnostic genetic test (96%, 50/52). Testing for a panel of genes (either linked to dementia/MND) was the next most common (31%, 16/52), followed by combined *GRN* and *MAPT* testing (10%, 5/52) and *SOD1* testing (8%, 4/52). As expected, *C9orf72* was the most frequent predictive test undertaken in unaffected relatives (87%, 47/54). *SOD1* and *TARDBP* were each 4% (2/54) of total predictive tests, while testing for *GRN, FUS* and *MAPT* variants each accounted for 2% (1/54).

Genetic counselling appointment data were available from 8/10 centres. Diagnostic test patients generally had between one to two genetic counselling appointments (mean 1.8), while predictive test patients tended to have three to four appointments (mean 3.9) inclusive of results appointments and any follow-up provided. Affected patients were also more likely to have seen neurology/psychiatry prior to clinical genetics 89% (62/70), compared to unaffected relatives 12% (28/231). Comparatively, only 9% (20/231) of unaffected relatives were referred on to neurology, this includes those that underwent predictive testing and were found to be carriers and also some individuals with neurological symptoms who did not undergo testing.

DISCUSSION

Genetic testing is undergoing rapid change owing to advances in sequencing technology. Within the UK, access to testing across England is now subject to criteria listed within the NHS Genomic Test Directory.[11] Relevant criteria for MND and FTD come under section 'R58

Adult onset neurodegenerative disorder'. On this basis, genetic testing in MND requires an ALS diagnosis with evidence of upper and lower motor neurone involvement, a progressive course and additionally either age of onset under 40 years or a MND/FTD family history. Given the mean age of onset for MND/FTD in *C9orf72* carriers is around 58 years, 40 years is likely too stringent a cut-off and risks denying diagnostic genetic testing to expansion carriers, especially as reduced and age-related penetrance frequently obscure dominant inheritance patterns.[12, 13] Similarly, current criteria for FTD (or otherwise unexplained dementia) require age of onset under 55 years or else family history of the same dementia type in a first- or second-degree relative. This again likely represents too strict an age limit and additionally does not allow for MND family history. Although our evaluation did not collect age of onset data, based on Test Directory family history criteria alone, only 10/22 diagnostically tested individuals with FTD (45%), 13/19 with MND (68%) and 2/3 with MND and FTD (67%) in our cohort would have been eligible for testing, while 20/44 (45%) diagnostically tested individuals would not have been tested on account of 16 having no family history and four having family history not meeting the criteria. Furthermore, five cases (4/13 with FTD and 1/3 with MND and FTD) in this cohort would not have had their pathogenic *C9orf72* expansions detected, suggesting the current criteria may only have a diagnostic sensitivity of around 71% (33% in FTD).

The genetics of MND and FTD is complex and evolving and the instigation of strict testing eligibility criteria as currently proposed may be premature. The paramount concern of any guidelines should be the best care and management of patients. Patients are of course individuals with their own specific circumstances and best practice requires that clinicians have flexibility to be able to treat them as such. This individuality is illustrated by the

proportions of affected and unaffected individuals opting for/against testing and the diverse number of genetic counselling appointments observed. The role of clinicians in these circumstances is to help patients make the best choice for themselves and their families regarding genetic testing. The testing of sporadic MND or FTD cases presents a particular challenge with respect to family implications and the need to consider testing in such patients is increasingly being recognised in neurology settings.[14, 15] In this regard, collaboration between clinical genetics and neurology is highly recommended and would best be provided via multidisciplinary clinics, whereby neurology could provide detailed phenotyping of affected patients and unaffected (but potentially oligosymptomatic) relatives and also advise on disease-specific management, while genetics could contribute expertise in pre- and post-test counselling, variant interpretation, reproductive options and wider family management. A further consideration is the development of novel therapies for MND/FTD, with clinical trials of antisense oligonucleotides for *C9orf72* and *SOD1* currently underway. Patients are increasing aware of these research developments, which can influence their desire to undergo testing. Chiò et al. proposed an MND genetic testing algorithm involving two-dimensions of clinical relevance and availability of effective treatments.[14] If new genetic therapies do become available, this will significantly impact the uptake of pre-symptomatic genetic testing. In summary, we propose an approach to genetic testing in MND and FTD that is flexible enough to take account of patient-specific differences and which relies on adequate genetic counselling.

1. Familial pathogenic variant known: offering targeted genetic testing on a diagnostic or predictive basis would be appropriate following adequate genetic counselling. For predictive testing this would usually involve a process akin to Huntington disease predictive testing.[16]

2. Affected individuals with autosomal dominant inheritance (allowing for incomplete penetrance): sequential testing of *C9orf72* followed by broader gene panel-based testing would be indicated following appropriate counselling. Such counselling must discuss not only personal and familial implications of the result but also possibility of incomplete penetrance, the phenotypic spectrum of disease and the potential for and implications of finding variants of uncertain significance (VUSs).

3. Affected individual without family history: diagnostic testing of *C9orf72* might be considered but a cautious approach is advisable and adequate genetic counselling essential. While *C9orf72* expansions occur in up to 7% of sporadic MND and up to 6% of sporadic FTD cases, population studies also suggest the expansion is present in 0.2-0.6% of North Europeans, a frequency some ten times greater than expected based on MND/FTD incidence, therefore indicating reduced penetrance.[17, 18] Sequencing other genes in sporadic cases remains problematic owing to difficulty interpreting VUSs and is therefore better avoided unless specific phenotypes suggest a genetic aetiology. In sporadic MND, *SOD1* pathogenic variants occur in 1-2% of cases, *TARDBP* and *FUS* pathogenic variants in around 1% each, with other genes implicated more rarely.[4] In sporadic FTD, *GRN* pathogenic variants occur in up to 5% of cases, *MAPT* in up to 3% and other genes more rarely.[19, 20] There therefore remains a significant chance of finding pathogenic variants should testing be undertaken. However, in sporadic cases the positive predictive value of subsequently testing for such variants in unaffected relatives is likely reduced, since additional unknown protective factors may exist in a family that could contribute to reduced penetrance. Such calculations depend greatly on individual family structure and are best considered on a case-by-case basis.

4. Unaffected relatives without known familial pathogenic variant: predictive genetic testing would not be considered appropriate given our limited understanding of penetrance, genetic heterogeneity and potential oligogenic effects.

REFERENCES

1 Logroscino G, Couratier P, Babron M, Leutenegger AL, Copetti M. Variation in worldwide incidence of amyotrophic lateral sclerosis: a meta-analysis. *Int J Epidemiol* 2017;**46**:57–74.

2 Byrne S, Walsh C, Lynch C, Bede P, Elamin M, Kenna K, Mclaughlin R, Hardiman O. Rate of familial amyotrophic lateral sclerosis: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2011;**82**:623–7.

3 van Es MA, Hardiman O, Chio A, Al-Chalabi A, Pasterkamp RJ, Veldink JH, van den Berg LH. Amyotrophic lateral sclerosis. *Lancet* 2017;**390**:2084–98.

4 Renton AE, Chiò A, Traynor BJ. State of play in amyotrophic lateral sclerosis genetics. *Nat Neurosci* 2014;**17**:17–23.

5 Rippon GA, Scarmeas N, Gordon PH, Murphy PL, Albert SM, Mitsumoto H, Marder K, Rowland LP, Stern Y. An observational study of cognitive impairment in amyotrophic lateral sclerosis. *Arch Neurol* 2006;**63**:345–52.

6 Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, Shaw PJ, Simmons Z, Van Den Berg LH. Amyotrophic lateral sclerosis. *Nat Rev Dis Prim* 2017;**3**:17071.

7 Burrell JR, Kiernan MC, Vucic S, Hodges JR. Motor neuron dysfunction in frontotemporal dementia. *Brain* 2011;**134**:2582–94.

8 Onyike CU, Diehl-Schmid J. The epidemiology of frontotemporal dementia. *Int Rev Psychiatry* 2013;**25**:130–7.

9 Rohrer JD, Beck J, Isaacs AM, Authier A, Warren JD, Mead S, Rossor MN. The heritability and genetics of frontotemporal lobar degeneration. *Neurology* 2009;**73**:1451–6.

10 Deleon J, Miller BL. Frontotemporal dementia. *Handb Clin Neurol* 2018;**148**:409–30.

11 National Health Service (NHS) England. National Genomic Test Directory: Testing Criteria for Rare and Inherited Disease. 2020.

12 Murphy NA, Arthur KC, Tienari PJ, Houlden H, Chiò A, Traynor BJ. Age-related penetrance of the C9orf72 repeat expansion. *Sci Rep* 2017;**7**:2116.

13 Moore KM, Nicholas J, Grossman M, McMillan CT, Irwin DJ, Massimo L, Van Deerlin VM, Warren JD, Fox NC, Rossor MN, Mead S, Bocchetta M, Boeve BF, Knopman DS, Graff-Radford NR, Forsberg LK, Rademakers R, Wszolek ZK, van Swieten JC, Jiskoot LC, Meeter LH, Dopper EG, Papma JM, Snowden JS, Saxon J, Jones M, Pickering-Brown S, Le Ber I, Camuzat A, Brice A, Caroppo P, Ghidoni R, Pievani M, Benussi L, Binetti G, Dickerson BC, Lucente D, Krivensky S, Graff C, Öijerstedt L, Fallström M, Thonberg H, Ghoshal N, Morris JC, Borroni B, Benussi A, Padovani A, Galimberti D, Scarpini E, Fumagalli GG, Mackenzie IR, Hsiung GYR, Sengdy P, Boxer AL, Rosen H, Taylor JB, Synofzik M, Wilke C, Sulzer P, Hodges JR, Halliday G, Kwok J, Sanchez-Valle R, Lladó A, Borrego-Ecija S, Santana I, Almeida MR, Tábuas-Pereira M, Moreno F, Barandiaran M,

Indakoetxea B, Levin J, Danek A, Rowe JB, Cope TE, Otto M, Anderl-Straub S, de Mendonça A, Maruta C, Masellis M, Black SE, Couratier P, Lautrette G, Huey ED, Sorbi S, Nacmias B, Laforce R, Tremblay MPL, Vandenberghe R, Damme P Van, Rogalski EJ, Weintraub S, Gerhard A, Onyike CU, Ducharme S, Papageorgiou SG, Ng ASL, Brodtmann A, Finger E, Guerreiro R, Bras J, Rohrer JD, Heller C, Convery RS, Woollacott IO, Shafei RM, Graff-Radford J, Jones DT, Dheel CM, Savica R, Lapid MI, Baker M, Fields JA, Gavrilova R, Domoto-Reilly K, Poos JM, Van der Ende EL, Panman JL, Donker Kaat L, Seelaar H, Richardson A, Frisoni G, Mega A, Fostinelli S, Chiang HH, Alberici A, Arighi A, Fenoglio C, Heuer H, Miller B, Karydas A, Fong J, João Leitão M, Santiago B, Duro D, Ferreira C, Gabilondo A, De Arriba M, Tainta M, Zulaica M, Ferreira C, Semler E, Ludolph A, Landwehrmeyer B, Volk AE, Miltenberger G, Verdelho A, Afonso S, Tartaglia MC, Freedman M, Rogaeva E, Ferrari C, Piaceri I, Bessi V, Lombardi G, St-Onge F, Doré MC, Bruffaerts R, Vandenbulcke M, Van den Stock J, Mesulam MM, Bigio E, Koros C, Papatriantafyllou J, Kroupis C, Stefanis L, Shoesmith C, Robertson E, Coppola G, Da Silva Ramos EM, Geschwind D. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. *Lancet Neurol* 2020;**19**:145–56.

14 Chiò A, Battistini S, Calvo A, Caponnetto C, Conforti FL, Corbo M, Giannini F, Mandrioli J, Mora G, Sabatelli M, Ajmone C, Mastro E, Pain D, Mandich P, Penco S, Restagno G, Zollino M, Surbone A, Monsurrò MR, Tedeschi G, Conte A, Luigetti M, Lattante S, Marangi G, Volanti P, Marinou K, Papetti L, Lunetta C, Pintor GL, Salvi F, Bartolomei I, Quattrone A, Gambardella A, Logroscino G, Simone I, Pisano F, Spataro R, La Bella V, Colletti T, Mancardi G, Origone P, Sola P, Borghero G, Marrosu F, Marrosu MG, Murru MR, Floris G, Cannas A, Piras V, Costantino E, Pani C, Sotgiu MA, Pugliatti M, Parish LD, Cossu P, Ticca A, Rodolico C, Portaro S, Ricci C, Moglia C, Ossola I, Brunetti M, Barberis M, Canosa A, Cammarosano S, Bertuzzo D, Fuda G, Ilardi A, Manera U, Pastore I, Sproviero W, Logullo F, Tanel R. Genetic counselling in ALS: facts, uncertainties and clinical suggestions. *J Neurol Neurosurg Psychiatry* 2014;**85**:478–85.

15 Turner MR, Al-Chalabi A, Chio A, Hardiman O, Kiernan MC, Rohrer JD, Rowe J, Seeley W, Talbot K. Genetic screening in sporadic ALS and FTD. *J Neurol Neurosurg Psychiatry* 2017;**88**:1042–4.

16 Macleod R, Tibben A, Frontali M, Evers-Kiebooms G, Jones A, Martinez-Descales A, Roos R, Bijlsma E, Blinkenberg E, Bombard Y, Borry P, Craufurd D, Davis M, De Die-Smulders C, Downing C, Dürr A, Garcia Barcina M, Glew R, Heiberg A, Heydon F, Hoffman-Zacharsk D, Hösterey Ugander U, José Trujillo Tiebas M, Krysa W, Liebaers I, Lohkamp C, Mandich P, Mariotti C, De Schepper B, Di Maria E, Nemeth A, Quarrell O, Ribaï P, Semaka A, Seneca S, Sequeiros J, Squitieri F, Sulek A, Van Der Meer L, Verellen-Dumoulin C, De Wert G, Delatycki M, Guttman M, Hayden M, Nance M, Richards F, Vetter L. Recommendations for the predictive genetic test in Huntington's disease. *Clin Genet* 2013;**83**:221–31.

17 Majounie E, Renton AE, Mok K, Dopper EGP, Waite A, Rollinson S, Chiò A, Restagno G, Nicolaou N, Simon-Sanchez J, van Swieten JC, Abramzon Y, Johnson JO, Sendtner M, Pamphlett R, Orrell RW, Mead S, Sidle KC, Houlden H, Rohrer JD, Morrison KE, Pall H, Talbot K, Ansorge O, Hernandez DG, Arepalli S, Sabatelli M, Mora G, Corbo M, Giannini F, Calvo A, Englund E, Borghero G, Floris GL, Remes AM, Laaksovirta H, McCluskey L, Trojanowski JQ, Van Deerlin VM, Schellenberg GD, Nalls M a, Drory VE, Lu C-S, Yeh T-H, Ishiura H, Takahashi Y, Tsuji S, Le Ber I, Brice A, Drepper C, Williams N,

Kirby J, Shaw P, Hardy J, Tienari PJ, Heutink P, Morris HR, Pickering-Brown S, Traynor BJ. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol* 2012;**11**:323–30.

18 Beck J, Poulter M, Hensman D, Rohrer JD, Mahoney CJ, Adamson G, Campbell T, Uphill J, Borg A, Fratta P, Orrell RW, Malaspina A, Rowe J, Brown J, Hodges J, Sidle K, Polke JM, Houlden H, Schott JM, Fox NC, Rossor MN, Tabrizi SJ, Isaacs AM, Hardy J, Warren JD, Collinge J, Mead S. Large C9orf72 hexanucleotide repeat expansions are seen in multiple neurodegenerative syndromes and are more frequent than expected in the UK population. *Am J Hum Genet* 2013;**92**:345–53.

19 Rademakers R, Neumann M, Mackenzie IR. Advances in understanding the molecular basis of frontotemporal dementia. *Nat Rev Neurol* 2012;**8**:423–34.

20 Olszewska DA, Lonergan R, Fallon EM, Lynch T. Genetics of Frontotemporal Dementia. *Curr Neurol Neurosci Rep* 2016;**16**:107.

FIGURE LEGENDS

Figure 1. A. Disease status of referred patients. B. Sources of the referrals included in this service evaluation. **C**. Prior known familial mutations from within this cohort of referred individuals. **D**. Numbers of affected individuals undergoing diagnostic genetic tests. "100KGP" refers to recruitment to the 100,000 Genomes Project; "Other" includes undergoing testing for spinocerebellar ataxia, dentatorubral-pallidoluysian atrophy, spinal and bulbar muscular atrophy and hereditary spastic paraplegia. **E**. Numbers of unaffected relatives undergoing predictive genetic testing for different genes. **F**. Total number of genetic counselling appointments attended by affected individuals undergoing diagnostic genetic testing. **G**. Total number of genetic counselling appointments attended by unaffected relatives undergoing predictive genetic testing.

Figure 2. Clinical genetics referral numbers and subsequent outcomes for individuals affected by MND or FTD and for unaffected relatives of affected individuals.

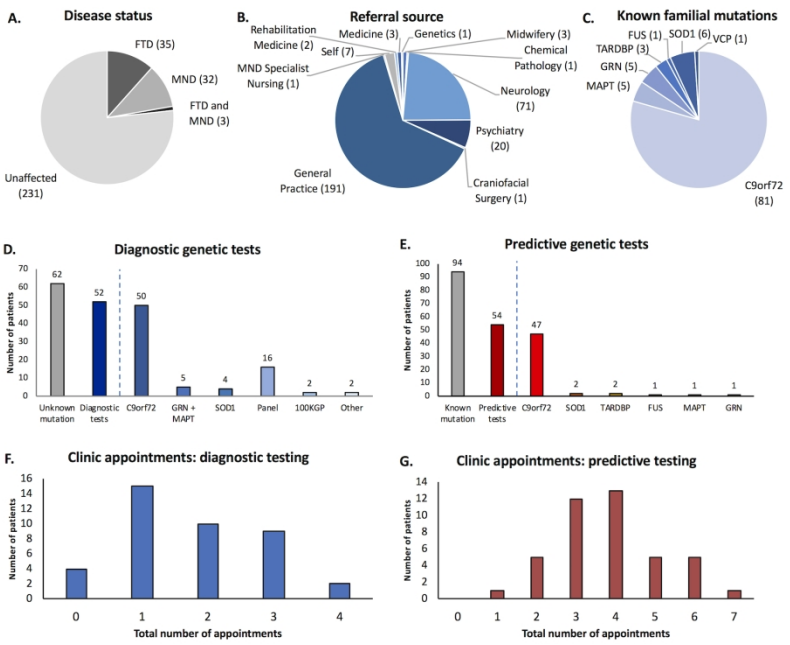

Figure 1. A. Disease status of referred patients. B. Sources of the referrals included in this service evaluation. C. Prior known familial mutations from within this cohort of referred individuals. D. Numbers of affected individuals undergoing diagnostic genetic tests. Of 62 patients with unknown mutations, 52 underwent testing in total and the breakdown of requested tests is shown in subsequent columns. "100KGP" refers to recruitment to the 100,000 Genomes Project; "Other" includes undergoing testing for spinocerebellar ataxia, dentatorubral-pallidoluysian atrophy, spinal and bulbar muscular atrophy and hereditary spastic paraplegia. E. Numbers of unaffected relatives undergoing predictive genetic testing for different genes. Of 94 patients with a known familial mutation, 54 underwent testing in total and the breakdown of these tests is shown in subsequent columns. F. Total number of genetic counselling appointments attended by affected individuals undergoing diagnostic genetic testing. G. Total number of genetic counselling appointments attended by unaffected relatives undergoing predictive genetic testing.

212x150mm (300 x 300 DPI)

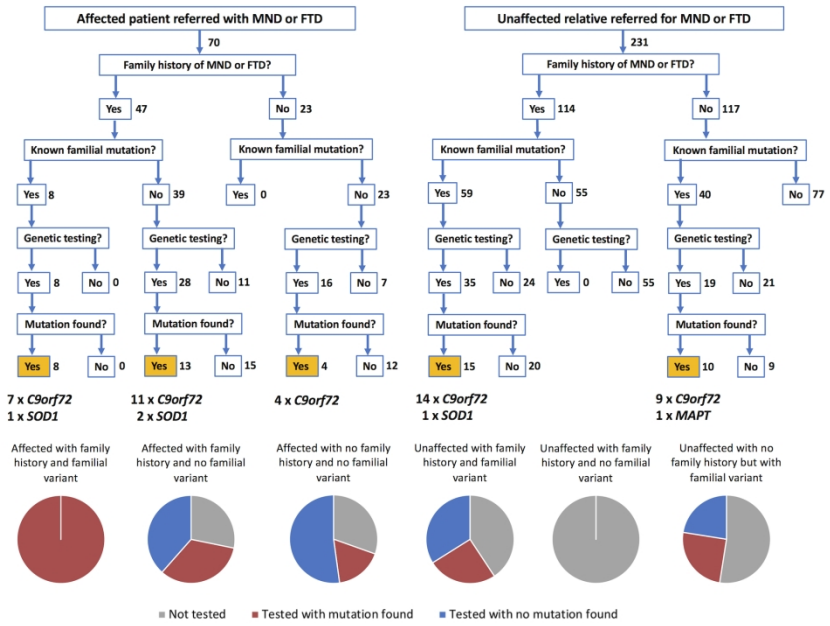

Figure 2. Clinical genetics referral numbers and subsequent outcomes for individuals affected by MND or FTD and for unaffected relatives of affected individuals.

212x150mm (300 x 300 DPI)