The futility boundary while waiting for the next confidence interval

Many of the terms used in research papers seem ripe for being repurposed for clinical practice. For instance, the P value could be a measure of how likely a urine dipstick is to change management for a patient with suspected urinary tract infection (usually <0.05). A confidence interval might be the part of the day, usually lasting about 20 minutes and never occurring after 11 am, when you feel that you’re doing a decent job. Crossing the futility boundary, instead of being the point at which they stop a trial early because the drug clearly doesn’t work, could be when you realise you’re not going to leave on time so there’s no point rushing.

Meanwhile, in a randomised controlled trial of pemafibrate versus placebo in over 10,000 patients with type 2 diabetes, high triglyceride levels, and low HDL cholesterol, an interim analysis found the “futility boundaries had been crossed” so the trial was ended early—and this is despite the primary endpoint being changed partway through the study in order to detect smaller effects sizes.

/Born002

IUA for OACGs

Unfamiliar abbreviations (UA) are a bugbear of mine—I’ve got a real bee in my bonnet (BIMB) about them. My BIMB got buzzing this week on reading a research letter about opioid analgesic and gabapentinoid co-prescribing. It included the UA for concurrent opioid analgesia and gabapentin episodes (OACG). That isn’t just an UA but also an illogical UA, or IUA, since the C is obviously in the wrong place. OACGs, defined as any overlap between opioid and gabapentinoid prescribing, have increased in the US, having occurred 1.9% of the time in 2016 but up to 7.6% in 2018.

Let’s hope raising awareness of this IUA (increase in unlicensed analgesia) succeeds in having a BIMB (big impact on medical behaviour).


Trial raising questions around transparency and generalisability

Recruiting people from low and middle income countries (LMIC) for clinical trials of new drugs whose findings are unlikely to be relevant for them (such as due to the high cost of the drug) is unethical and raises serious questions about the generalisability of the findings. Despite that, a new cross-sectional analysis of pivotal trials for 66 recently FDA-approved drugs for cancer, neurological disease, and cardiovascular disease between 2012 and 2019 found that most of the pivotal trials recruited from LMICs—as high as 79% of those for drugs for cardiovascular disease.

Transparency was also an issue: from the 144 pivotal trials identified, country level involvement data were not available for 71 (55%) of them.

/JAMA Intern Med doi: 10.7326/M22-1857

Bacterial causes of death

A systematic analysis in the Lancet reminds us how common death from infection (specifically bacterial infection) is. It estimates that in 2019 there were 13.7 million infection related deaths, with 7.7 million deaths from one of 33 bacteria included in the study. This was the second leading cause of death globally. The age standardised mortality rate from these bacteria varied according to location: four times higher for those living in sub-Saharan Africa than in high income regions, for example.

The most deadly bacterium in the report is Staphylococcus aureus, the leading bacterial cause of death in 135 countries and in people over 15 years old.

/Lancet doi: 10.1016/S0140-6736(22)02185-7

Morphine for breathlessness

Opioids are recommended in the palliative care setting as an option to consider for managing breathlessness. In patients with advanced COPD, who experience chronic breathlessness at rest or on minimal exertion, previous trials have suggested that low dose opioids might help some people’s symptoms.

However, findings from a new randomised control trial of people with COPD and a modified MRC breathlessness scale score of 3 or 4 do not support use of low dose opioids in this group. It found that, compared with placebo, 8 mg or 16 mg of oral extended release morphine per day had no effect on the primary endpoint of the intensity of participants’ worst breathlessness after a week.


Tom Nolan, clinical editor, The BMJ, London; sessional GP, Surrey

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Adapting to transparent medical records: international experience with “open notes”

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By 30 November 2022, patients in England who sign up for online services such as the NHS App1 should have access to their full primary care health record prospectively and by default.2 Every new entry made in the primary care record will be immediately visible to patients, including the free-text consultation entries (commonly referred to as “open notes”). Clinicians are understandably concerned about this radical change in practice, fearing additional burdens for their work, an onslaught of calls or emails from anxious or confused patients, and potential risks to patients’ safety.3,4

In this article we summarise concerns and offer suggestions for how clinicians may consider changing their practice.

Background to open notes

The move to share access to clinical records signals a more equal partnership between patients and clinicians. In adopting this innovation, England follows other countries such as Sweden and the US, where both experiences of clinicians, before and after patient access, and patients’ experiences with reading their notes have attracted scrutiny.38-40

In England, since April 2019 the GP contract committed practices to offer full online access on a prospective basis to new patients—that is, from the date patients request it.41 Notably, by July 2022, 48.1% of patients had signed up for at least one service, but only 13.7% were able to view their detailed coded record.42 Information regarding the percentage of patients with full access to their records—including free-text consultation entries—is not publicly available, but currently the level of access granted varies and is a source of frustration for patients.43

Clinicians’ concerns

As movement towards transparency accelerates in different countries and health systems, surveys and qualitative studies show primary care staff share many questions about the practice of open notes. These concerns seem to cut across national boundaries and health systems.4-10 44-50

The table summarises concerns commonly raised by clinicians, and the current evidence for each of these. These findings come with several caveats. They focus on the perceptions of clinicians and patients who use open notes, and findings dependent on self reporting can be unreliable. The data draw primarily on small numbers of medical centres and hospitals, limiting the generalisability of the results. Moreover, the findings may over-represent respondents with positive or negative biases about patient access to clinical notes.

More robustly representative surveys and studies that include objective measures of the effects of open notes on documentation, clinician workflow, and patient outcomes have yet to emerge.23,31,12 From both patient and clinician perspectives, many challenges and unknowns persist, and it will be crucial to learn more about the consequences of shared notes as more experience emerges.

WHAT YOU NEED TO KNOW

• By 30 November 2022, patients in England who have signed up for an online service such as the NHS App should have prospective access to their primary care health record enabled by default. Access includes GPs’ free-text consultation entries (commonly referred to as open notes)

• GPs may have concerns about open notes, a practice that has now been implemented in several countries. To date, preliminary findings show that many reported worries disappear with experience.

• Doctors can empower patients and themselves by implementing a number of techniques and practices in preparation for patient access to their notes.
Recommendations to prepare for open notes

We offer 10 suggestions to help GPs, the wider primary care team, and patients prepare for this change of practice.135-66 Reviewed and informed by a panel of six patients (see “How patients were involved in the creation of this article”), these recommendations are designed to help physicians optimise the potential benefits of open notes and minimise their risks (see also box 1, a guide for patients, and box 2, what patients find helpful, on bmj.com).

Educate patients and staff about open notes

- Inform patients that open notes can be empowering and can help them feel more in control of their health care.
- Advise patients that, by actively reading notes, they may both clarify their health goals and partner more effectively with their doctor.
- Suggest to patients that reading notes may foster greater understanding of the reasons for treatments and medications and help them, their family, and other care partners to remember and follow the next steps in their care plan.
- Include links to patient information materials in the record that patients can read at home, such as https://www.bad.org.uk/patient-information-leaflets
- Share information about open notes with practice staff, including non-clinical staff, who may require training in how to manage queries from patients.

Involve patients in what you write and create a shared plan of action

- When possible, and providing there are no safeguarding concerns, turn the computer screen towards patients to show them what you are documenting, or offer to read it aloud. Ask if there is anything they would like you to add.
- To ensure understanding, if you cite a diagnosis in the notes, discuss it with the patient and, where appropriate, their care giver.
- Incorporate into notes patients’ health decisions and their reasons for their choices.
- Avoid directive language that may point to the role of an authoritative doctor; such as “Patient was told to …” “I have instructed her to do …”
- Use second person voice to reflect collaborative decisions; such as “We will work together as a team,” “We discussed …”

Avoid medical jargon or potentially offensive acronyms. Eg, use “follow-up” instead of “F/U”

- Use notes to celebrate patients’ strengths and progress; such as “Congratulated on stopping smoking.” When addressing areas in which patients may feel they are failing, balance the discussion with positive statements.

Write entries with empathy and sensitivity

- Assume that patients read their notes, even if they do not discuss what they have read in consultations.
- Avoid medical jargon or potentially offensive acronyms. For example, use “follow-up” instead of “F/U”; “shortness of breath” instead of “SOB.” Where available, use inbuilt software tools to convert acronyms to full text.15
- Avoid references to patients that may be perceived as judgmental or offensive; such as “Patient non-adherent/complaining about/denied/stated/refused.”
- Discuss or avoid potentially difficult terms. For example, for patients with obesity, omit or place that word in the context of body mass index and health risks, rather than as a sole descriptor that may be viewed as pejorative.
- Avoid stigmatising language, including reference to patients’ diagnoses or health status (such as “drug user”) or to their progress or demeanour (such as “he insists that,” “in denial,” “difficult patient,” “failed to”).

Explain that free-text entries serve multiple functions

- Explain the multiple purposes of the medical record to patients.
- Although patients will now read their notes, do not leave out appropriate differential diagnoses. Discuss your logic and sense of probabilities with them.

Strive to ensure that patients are not surprised by what they read.

- Encourage patients to ask about entries they may not understand.

Address risks and possible unintended consequences.

- During consultations, talk about diagnostic possibilities with patients. For example, “It’s extremely unlikely that this is a cancer, but we wouldn’t want to miss it, so I’m adding it to my list of possibilities. It’s far down my list—it’s much more likely to be X.”
- Discuss with patients the emotional risks versus benefits of reading their notes. Some may decide not to read them, thereby avoiding potential upset.
- Talk to colleagues about best practice regarding safeguarding and confidentiality. Set up a protocol for practice staff to follow if patients report upset or anxiety.

Support marginalised populations

- Do not assume more vulnerable or disadvantaged patients will not benefit from, or “handle,” reading their notes.
- Consider what steps your practice can take to maximise accessibility and inclusion. For example, offer “How to get online” guides to the practice website. Work with local charities and patient participation groups to provide additional local support.

Offer help about proxy access, safeguarding, and privacy

- Advise adolescents and at-risk individuals about the importance of privacy and confidentiality.
- Safeguard against revealing third party information by advising patients you can use a separate and hidden entry to record sensitive information they would prefer not to be visible in their online record.
- To protect the privacy of their records, remind patients to adopt safe practices around password protections, especially on shared electronic devices.
- Inform patients they can ask their GP to turn off open access, so that only their GP and other clinicians can view their record.
- Offer advice about maintaining privacy via the practice website, surgery posters, and in person.
Ask patients for feedback and manage disagreement at the earliest opportunity

- Do not assume that, without active encouragement, patients will be comfortable offering feedback on perceived errors in the medical record.
- Be open about the fact that errors and omissions can happen in records. Be proactive in encouraging patients to help spot errors so they can be rectified.
- Create a practice protocol for processing disagreements.
- If disagreements are not resolved, ask patients to work with you to document their view as an additional note. For example, “Discussed difference of opinion. [Patient’s name] would like me to note that . . .” [66-67]

Remind patients to check their records before and after appointments

- Encourage patients to review their notes before visits, both to refresh their memory and to be prepared to discuss any concerns.
- Add reminders to do this via the practice website, surgery posters, and in person.
- Incorporate reminders to patients to read records via GP phone messaging systems, and/or integrate such reminders into text messages about appointments.

Raise awareness of open notes

- Do not assume patients know they can access their primary care records online.
- The consultation is the most powerful place to inform patients about open notes.
- Advise patients where they can learn more about the NHS App and other platforms they can use to access their notes. [67]
- Adapt the illustrative patient guidelines to your practice (box 1 on bmj.com) and adopt other methods to publicise online access via the surgery website, and by posters and leaflets in waiting rooms.

Competing interests

See bmj.com.

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Find the full version with references at doi: 10.1136/bmj-2021-069861

EDUCATION INTO PRACTICE

- Consider how you might talk to patients about access to their clinical notes. Ask what else can be done to help patients prepare for reading their notes.
- Reflect on how access could be used as a means of empowering patients and enhancing shared decision-making.

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### Clinicians’ concerns about open notes and current evidence

<table>
<thead>
<tr>
<th>Clinicians’ concerns</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>Open notes will add to workload and increase inefficiencies</td>
<td>NHS Digital stated: “Early adopter sites [in England] reported that, when switching on prospective access for their patients, they did not see an increase in workload.” [46] In a recent US study of 116 primary care physicians, 69%, before adopting open notes, anticipated spending more time addressing patients’ questions outside of consultations. After implementation, only 8% reported having done so. [47] Such findings are similar to those in prior studies, [11,12] but in another recent US survey, 62% (n=468) of physicians reported spending the same amount of time writing notes after patient access was enabled, whereas about a third reported taking more time. [12]</td>
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<tr>
<td>Access could have complex implications for patient safety, especially for patients at particular risk</td>
<td>When and how clinicians can appropriately redact information without contributing to stigmatisation or harm is a difficult issue for practices. [13] Some suggest it may be resolved by adapting current software architecture to support clinicians’ discretion about how to prevent harm. [13] Clinicians in Sweden and the US report recording two entries in situations where patients or third parties are at risk of serious physical harm (such as a vulnerable patient in a coercive relationship who has shared information): one for the patient, and another for clinicians. In September 2022, NHS Digital reported that “Early adopter sites [in England] were asked to report immediately any clinical safety incidents or near misses, lessons, risks and issues and concerns,” and “No incidents or near misses have been reported to date by early adopter sites.” Access to notes may function as a safety mechanism. [15-17] In a multicentre survey in the US, among 22,000 patients who read their notes, one in five reported an error, and 40% of those patients perceived the error to be serious. [18] Their reports included inaccurate medical history and diagnoses, wrong patient’s notes, and wrong-sidedness.</td>
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<tr>
<td>Patients may be harmed emotionally by what they read, and this could affect their behaviour</td>
<td>Evidence of emotional harm is lacking; in the largest survey of open notes in the US, involving more than 22,000 patients in three diverse health systems (response rate 22%), most (16354/22520, 73%) reported that access was very important for helping take care of their health. [19] Two thirds of those taking medications who read at least one note in the previous 12 months reported greater understanding of their medication regimen, and 14% of those surveyed reported improved adherence, [20] a figure that rose to 20% among patients diagnosed with serious mental health conditions. [11] An underappreciated consideration may be anxiety and confusion caused by lack of ready access to notes. [12]</td>
</tr>
<tr>
<td>Documentation will be &quot;dumbed down,&quot; reducing its clinical value</td>
<td>Reports assessing whether changes in documentation accompanying open notes diminish their value to other health professionals have not been published, [12] but in a US survey, 77% (n=188) of primary care physicians perceived no change in the value of their notes for other clinicians. [12]</td>
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<tr>
<td>Patients will feel judged or offended by what they read, thereby undermining the patient–doctor relationship</td>
<td>Some patients report access to notes builds greater trust. Dr Amir Hannan, successor in 2007 to the practice where Dr Harold Shipman worked, found that offering patients access to open notes helped establish a “partnership of trust.” [21] In a three-centre study in the US, most patients reported unchanged or increased trust in their doctor after reading their notes, and many described enhanced teamwork and shared goal alignment with their clinicians. [22] However, in the same study, 24.1% patients (10.5%) reported feeling judged or offended by something they read. [23] They described feeling labelled and/or disrespected, or finding something surprising or erroneous in a note. In other single-centre qualitative studies, patients who report discrepancies between what was discussed during appointments and what was later documented also indicated strained trust in their clinicians. [24-26]</td>
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<tr>
<td>Patients will contest or disagree with their notes</td>
<td>Research into patients directly contesting or disagreeing with their notes is limited. In a US survey, among 4,500 survey respondents who read at least one medical note during a 12 month period, about a third reported that checking for accuracy was the principal reason for reading their notes. [19] Among the 7% (331/4592) of patients who reported contacting their physician’s office about a concern, 66% (220/331) reported that accessing notes increased trust and teamwork. [19-29] In a recent US survey, 62% of patients reported spending the same amount of time writing notes after patient access was enabled, whereas about a third reported taking more time. [12]</td>
</tr>
<tr>
<td>Access will increase risk for litigation</td>
<td>We are aware of no medical malpractice cases that have arisen in the US because of open notes. If clinicians make changes that reduce the quality of documentation and lead to error, risks of malpractice suits might increase. [22] However, if patient access helps reduce errors or diagnostic delays (the leading causes of claims [20,21]), this could reduce the risk of malpractice suits.</td>
</tr>
<tr>
<td>Health inequities will become be magnified</td>
<td>In several US surveys, patients who are older, less educated, who identify as being from racial or ethnic minorities, or whose first language differs from their provider are less likely to use online record access platforms. [19] However, when patients from these demographic groups gain access to notes, they report greater benefits from shared notes than do their counterparts, including increased trust and teamwork. [23-25] In the US, recent analyses indicate that negative patient descriptors in notes are significantly more common for non-Hispanic black patients and for patients with diabetes, substance use disorders, and chronic pain. [26,27]</td>
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Assessment of suspected motor neuron disease

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Motor neuron disease (MND) represents a group of neurodegenerative disorders that feature progressive motor weakness of limb or bulbar muscles (ie, those innervated by the lower brain stem). Classically, three distinct MND phenotypes are described, and these present along a spectrum of upper and lower motor neuron dysfunction,1 with increasing recognition of non-motor features.2

Amyotrophic lateral sclerosis (ALS) represents 85% of all MND cases, and features a combination of upper and lower motor neuron dysfunction.1 Primary lateral sclerosis (PLS) presents with upper motor neuron dysfunction, with substantial muscle spasticity. Primary muscular atrophy (PMA) presents with lower motor neuron dysfunction, with flaccid weakness and muscle atrophy. ALS is typically associated with rapid clinical decline, with survival typically 3-4 years from symptom onset, but PMA and more so PLS are associated with longer survival.3 This article focuses primarily on ALS.

WHAT YOU NEED TO KNOW

• Amyotrophic lateral sclerosis (ALS, a form of motor neuron disease) was previously considered rare, but incidence is expected to increase by 30% by 2040
• ALS is a multisystem disease that commonly causes cognitive and behavioural changes; up to one quarter of patients meet the criteria for dementia
• Diagnostic delay may reduce access to treatment and support that could improve survival and quality of life; refer urgently for expert assessment patients with asymmetrical painless progressive weakness or unexplained changes to swallowing

Why should non-neurologists know about ALS?

People with ALS often experience challenges in getting the right diagnosis (box). Most patients visit their general practitioner first, typically with mild symptoms such as cramps, balance disturbance, reduced dexterity, or subtle cognitive changes including apathy. The time from symptom onset to diagnosis ranges from 10 to 16 months, and signs often go unrecognised, with patients referred to other specialists or given misdiagnoses.3 Despite attempts to improve awareness in primary care, many doctors remain unfamiliar with the core features of ALS.6

Patients are often given a diagnosis of degenerative spinal disease, with 12% of ALS patients undergoing inappropriate surgery,7 which may lead to accelerated functional decline,8 increased levels of distress and anxiety for patients and their carers,9 and higher costs for health systems.10 Guidelines from the National Institute for Health and Care Excellence,11 European Academy of Neurology,12 and American Academy of Neurology13 emphasise early recognition and priority referral to an experienced centre for assessment. This allows early access to disease modifying therapies, clinical trials, and multidisciplinary support, which may improve survival and quality of life. Primary care doctors, as the gateway to medical contact, can be critical in reducing delays.

How common is ALS?

MND/ALS is a rare disease with a global prevalence of around 4.5 cases per 100 000, increasing to 12 to 15 per 100 000 in high income settings,14 comparable to the prevalence of glioblastoma multiforme, the most common malignant brain tumour.15 ALS presents most commonly in the sixth and seventh decades of life and is 1.3 times more common in men than women.16

In 2016, global deaths from ALS increased by 8%, rising to 14% in countries with a high sociodemographic index (SDI), and 22% in nations with a moderate SDI.16 By 2040, global incidence of ALS is estimated to increase by 31%, and by 50% in China and Iran.17

What causes ALS?

For most people, ALS occurs sporadically. Around 10% develop it as a result of mutations in chromosome 9 open reading frame 72 (C9orf72), or less commonly the superoxide dismutase 1 (SOD1) gene.18 In approximately 15% of patients with no reported family history the cause is eventually determined to be genetic, highlighting the

PATIENT INVOLVEMENT

RS provided a personal reflection as a patient and supplied guidance as to the priorities of those living with motor neuron disease. He provided critical review and revision of the manuscript.
Around 30% of individuals present with bulbar onset ALS with a combination of progressive dysphagia and dysarthria, sometimes referred to as progressive bulbar palsy. Dysphagia for dry crumbly food or thin liquids is common; however, subtle symptoms may include unexplained weight loss or increased eating time. Dysarthria may manifest as a change in diction or pitch, with hypernasality depending on the extent of upper or lower motor neuron involvement. A recognised molecular link exists between frontotemporal dementia (FTD) and ALS, resulting in 10-15% of patients presenting with significant behavioural and cognitive disturbances either before or alongside their motor weakness.

Environmental risks may be another contributing factor. One systematic review suggests that some individuals with high lifetime levels of physical activity (notably those playing professional sports with recurrent concussive or cervical traumas) are at an increased risk of disease.

**How does ALS present?**

ALS is a syndrome of initially localised, typically painless and progressive weakness, though different patterns of upper and lower motor neuron dysfunction may occur (fig 1). Limb onset ALS occurs in around 60% of patients, with asymmetric muscle weakness and atrophy occurring, often in the dominant limb, before spreading to the contralateral limb. Seventy per cent of patients present with limb weakness, approximately half with shoulder girdle and intrinsic hand muscle weakness, and half with asymmetric lower limb weakness.

Around 30% of individuals present with bulbar onset ALS with a combination of progressive dysphagia and dysarthria, sometimes referred to as progressive bulbar palsy. Dysphagia for dry crumbly food or thin liquids is common; however, subtle symptoms may include unexplained weight loss or increased eating time. Dysarthria may manifest as a change in diction or pitch, with hypernasality depending on the extent of upper or lower motor neuron involvement. A recognised molecular link exists between frontotemporal dementia (FTD) and ALS, resulting in 10-15% of patients presenting with significant behavioural and cognitive disturbances either before or alongside their motor weakness.

**2020 Gold Coast Criteria for ALS**

**Criteria for diagnosis of ALS**

- Progressive motor impairment documented by history or repeated clinical assessment, preceded by normal motor function, and
- Presence of upper and lower motor neuron* dysfunction in at least one body region,** (with upper and lower motor neuron dysfunction noted in the same body region if only one body region is involved) or lower motor neuron dysfunction in at least two body regions, and
- Investigations excluding other disease processes.***

*May be either clinical examination findings or features of active and chronic denervation using needle electromyography (EMG)

**Body regions are bulbar, cervical, thoracic, and lumbar/sacral

***The table lists suggested investigations to exclude other disease processes
What examination findings should prompt consideration of ALS?
The combination of upper and lower motor neuron findings in a limb or the bulbar region (eg, a wasted tongue and presence of a jaw jerk) should prompt consideration of ALS. The presence of a split hand (fig 2) has a high specificity (around 95% compared with healthy controls) for ALS, and is characterised by wasting of the lateral (thenar) side of the hand and preservation of the medial (hypothenar) side. Patients may develop widespread fasciculations, often more obvious proximally, though fasciculations in the absence of weakness should be interpreted with caution as this is common in healthy individuals.

Upper motor neuron dysfunction may manifest more subtly, with spastic (“high pitched”) dysarthria, slower walking, and impaired fractioned finger movements, accompanied by clonus, hyperreflexia, and extensor plantar responses. Cognitive and behavioural disturbance is increasingly recognised in ALS, and combined with motor dysfunction, substantial apathy, disinhibition, or emotional lability is linked with frontal lobe dysfunction associated with ALS-FTD spectrum disorder.

Does ALS affect only muscles?
Up to half of those with ALS develop some cognitive impairment, with 25% eventually meeting the criteria for FTD. The commonest cognitive and behavioural abnormalities are executive dysfunction and apathy, respectively, both being associated with poorer survival. Eighty per cent of patients experience significant anxiety and 20% develop psychosis. Screening for these symptoms should be routinely considered; the Edinburgh cognitive and behavioural ALS screen takes around 10 minutes to complete. Other non-motor symptoms may include hypermetabolism associated with weight loss, sleep disruption, and autonomic dysfunction.

What other conditions should be considered?
Up to two thirds of patients receive an alternative diagnosis prior to ALS; however, only 6% of those with ALS subsequently receive an alternative diagnosis. In those without a combination of upper and lower motor neuron signs, an alternative diagnosis should always be considered. The list of disorders that may mimic ALS is extensive;

**DIFFERENTIAL DIAGNOSES OF ALS, WITH CLINICAL PHENOTYPES AND SUGGESTED INVESTIGATIONS**

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Clinical phenotype</th>
<th>Helpful test</th>
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<tbody>
<tr>
<td>Multifocal motor neuropathy</td>
<td>Highly asymmetric and upper limb wasting with distal weakness</td>
<td>Nerve conduction study (conduction block) Anti-ganglioside antibodies</td>
</tr>
<tr>
<td>Cervical spondylotic myeloradiculopathy</td>
<td>Significant sensory symptoms +/- urinary dysfunction</td>
<td>Magnetic resonance imaging cervico-thoracic spine</td>
</tr>
<tr>
<td>Immune/inflammatory myopathy</td>
<td>Very high creatine kinase</td>
<td>Myositis associated antibody panel EMG Muscle biopsy</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Symptoms worsen as day progresses, periods of symptom remission. Bulbar weakness with ptosis</td>
<td>Anti-acetylcholine receptor antibodies Muscle specific kinase antibodies Repetitive nerve stimulation</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td>Weakness of finger flexors (typically spared in ALS)</td>
<td>Muscle biopsy Anti-NT5C1A antibodies EMG</td>
</tr>
<tr>
<td>Kennedy’s disease (spinobulbar muscular atrophy)</td>
<td>Male sex Fasciculations and wasting of tongue Gynaecomastia/testicular atrophy</td>
<td>Gene testing for mutation in androgen receptor (AR) gene</td>
</tr>
<tr>
<td>Peripheral nerve hyper-excitability syndrome</td>
<td>Prominent cramps and fasciculations without substantial weakness</td>
<td>Voltage gated potassium channel antibodies EMG to assess for spontaneous motor unit activity</td>
</tr>
<tr>
<td>Toxic/heavy metal neuropathy</td>
<td>Wrist and finger flexor weakness</td>
<td>Heavy metal studies Nerve conduction studies</td>
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**EDUCATION INTO PRACTICE**

- A 62 year old man presents with several months of progressive swallowing difficulties, weight loss, and difficulty doing up shirt buttons. What first steps will you take to explore his symptoms and condition?
- You are notified that a patient has received a diagnosis of ALS. What key areas will you prioritise for their future care?
Initially localised Limb (60%) typically asymmetric
Bulbar (30%) voice changes, swallowing
Early behavioural change (10%)

Painless, progressive weakness
Clinical suspicion of ALS from history
Concerning examination findings

Clinical suspicion of ALS from history

Non-motor findings
Wasted tongue and brisk jaw jerk
Muscle wasting
Presence of UMN and LMN signs
Muscle wasting
Wasted tongue and brisk jaw jerk
Muscle wasting
Focal but beyond one nerve root
Split hand sign (fig 2; “95% specific”)
Widespread fasciculations
More obvious proximally
Non-motor findings
Apathy, disinhibition or emotional liability

Blood tests
Haematology, biochemistry, thyroid function,
B12 and folate, immunoglobulins/protein electrophoresis
Spinal neuroimaging
NCS and EMG
Multidisciplinary clinic evaluation
Routine investigations
Referral to neurology
Investigations
NCS and EMG

Fig 3 | Left, coronal view of the brain in a patient with ALS. Green chevrons indicate the presence of increased signal (brightness) within the corticospinal tract, which may be seen in around 50% of ALS patients. Right: compression of the cord at C6/7 resulting in cervical myeloradiculopathy. This may mimic ALS with potentially lower motor neuron signs in the upper limbs and upper motor neuron signs in the lower limbs. This highlights the importance of obtaining spinal neuroimaging (preferably magnetic resonance imaging) in those with suspected ALS

Fig 4 | Proposed algorithm for prompt consideration of ALS as a diagnosis. UMN=upper motor neuron; LMN=lower motor neuron; B12=vitamin B12; NCS=nerve conduction studies; EMG=electromyography

However, several of the disorders are treatable or less aggressive than ALS, and these often have distinguishing clinical features (table, fig 3).

What tests should be considered when suspecting ALS?
The 2020 Gold Coast diagnostic criteria (box 1) emphasise that ALS is a clinical diagnosis. These criteria have a sensitivity greater than 90% for diagnosing ALS and stress that appropriate investigations should be undertaken to exclude other causes. Other investigations should be guided by the clinical history and examination.

What is the role of the non-neurologist in caring for those with ALS?
Management of ALS is complex, with patients relying on a range of health professionals to provide care. An ALS multidisciplinary clinic has a central role in facilitating care, and can provide a survival benefit of around eight months. The configuration of these services varies, but often involves physiotherapy, speech and occupational therapists, respiratory medicine, and palliative care. Specialist nurses provide a link with community services and general practice.

Specific therapies delivered by non-neurologists include non-invasive ventilation, with one cohort study showing that, in treated patients, median tracheostomy-free survival was 28 months compared with 15 months in untreated patients, with the greatest benefits seen in bulbar onset ALS. Improved nutritional support with high calorific fatty diets offered survival benefits in those with fast progressing disease. A combination of disease modifying and supportive therapies represent best practice in improving survival and quality of life for those with ALS; however, further well designed trials are needed to confirm the benefits.

Future developments
A major research focus in neurodegenerative disease is to identify prodromal or early disease, the hypothesis being that earlier disease modification will improve outcomes. The updated Gold Coast diagnostic criteria enable earlier diagnosis and access to emerging therapies. In future, non-motor features may also be incorporated. Biomarkers, such as serum neurofilament light chain, are elevated early in the disease and may also have a role in early diagnosis. ALS is a heterogeneous disease, and it is likely that analysis of a variety of clinical, genetic, and other biomarker profiles will lead to a more individualised approach to both prognosis and treatment. Until these techniques are translated into the clinic we will continue to rely on clinicians’ recognition of ALS.

We propose a simple clinical algorithm (fig 4) to highlight core clinical features to aid non-neurologists in recognising ALS and lead to prompt onward referral to an appropriate diagnostic service. The move towards precision medicine in ALS is being supported by global consortiums, such as the European Network to Cure ALS and the Northeast ALS Consortium in the US. With prompt diagnosis, patients have increasing opportunities to engage with these networks, whose ultimate aim is to identify disease modifying therapies to slow or halt disease progression.

Competing interests: None declared.

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A woman in her 60s presented with acute onset numbness and weakness of the left arm and leg for three days on a background of fatigue and weight loss without headache over six months. She took ramipril for hypertension but was normally well. She was admitted under the care of the acute stroke team, and magnetic resonance imaging of the brain confirmed right middle cerebral artery territory infarction. Initial investigations also revealed biochemical evidence of inflammation (table). Neither atrial fibrillation nor carotid artery stenosis (on Doppler ultrasound) were identified as causes for her stroke.

Empirical treatment for infective endocarditis was initiated, given the combination of lethargy, weight loss, raised inflammatory markers, and ischaemic stroke. However, blood cultures and transthoracic echocardiography were subsequently normal. Physical examination and computed tomography (CT) of thorax-abdomen-pelvis did not show any signs of malignancy, and there were no signs of vasculitis on focused review of the CT. Whole body fluorodeoxyglucose (FDG) positron emission tomography (PET) was performed (figure).

What caused this patient’s stroke?

Submitted by Jacob Day and Daniel Lashley

Patient consent obtained.

Cite this as: BMJ 2022;379:e066326

ENDGAMES

SPOT DIAGNOSIS

An unusual cause of stroke

A woman in her 60s presented with acute onset numbness and weakness of the left arm and leg for three days on a background of fatigue and weight loss without headache over six months. She took ramipril for hypertension but was normally well. She was admitted under the care of the acute stroke team, and magnetic resonance imaging of the brain confirmed right middle cerebral artery territory infarction. Initial investigations also revealed biochemical evidence of inflammation (table). Neither atrial fibrillation nor carotid artery stenosis (on Doppler ultrasound) were identified as causes for her stroke.

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RESULTS OF INITIAL INVESTIGATION OF PATIENT

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/L)</td>
<td>89</td>
<td>120-155</td>
</tr>
<tr>
<td>White blood cell count (+10^9/L)</td>
<td>11.2</td>
<td>3.6-9.2</td>
</tr>
<tr>
<td>Platelets (+10^9/L)</td>
<td>890</td>
<td>140-400</td>
</tr>
<tr>
<td>C reactive protein (mg/L)</td>
<td>140</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Plasma viscosity (mPa.s)</td>
<td>2.38</td>
<td>1.48-1.72</td>
</tr>
</tbody>
</table>

What caused this patient’s stroke?

Large vessel vasculitis—indicated by increased tracer uptake throughout the thoracic and abdominal aorta, with extension into bilateral subclavian, axillary, carotid, iliac, and femoral arteries on FDG PET scan (figure).

This inflammation of the aorta and its major branches can be due to either granulomatous or non-granulomatous inflammation. The term ‘large vessel vasculitis’ is commonly used to describe this condition, which is characterised by systemic symptoms and involvement of the aorta and its major branches.

When was this patient’s stroke?

Submitted by Jacob Day and Daniel Lashley

Patient consent obtained.

Cite this as: BMJ 2022;379:e066326
**MINERVA**

**Squamous cell carcinoma arising in smallpox vaccination scar**

This is a red macule with thick scales on the left arm of a man in his 60s. The patient had been vaccinated for smallpox at the site more than 40 years previously. For six months the itchy lesion had developed over the scar and had not improved with intermittent use of different topical steroids. A skin biopsy confirmed squamous cell carcinoma. Smallpox immunisation with vaccinia virus leaves a slightly depressed, smooth scar at the site of vaccination. Although rare, benign and malignant tumours have been reported at these vaccination sites, such as squamous cell carcinoma, basal cell carcinoma, melanoma, dermatofibrosarcoma protuberans, and malignant fibrous histiocytoma.

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Patient consent obtained.

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If you would like to write a Minerva picture case, please see our author guidelines at bit.ly/29HCBAL and submit online at bit.ly/29yyG6x

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**Long term effects of covid-19 pneumonia**

Persisting structural lung abnormalities after covid-19 pneumonia seem to be infrequent. Eighty four people who had survived covid-19 pneumonia severe enough to require hospitalisation, but not severe enough to need intubation or mechanical ventilation, were investigated using high resolution computed tomography scanning a year later. Lung abnormalities had completely resolved in 78 of the participants (Radiology doi:10.1148/radiol.220019).

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**Renal denervation**

Randomised controlled trials have shown that renal denervation carried out by radiofrequency ablation via a catheter induces a modest fall in blood pressure. A registry study suggests that the procedure leads to a useful reduction in the risk of cardiovascular events. Among 3000 people with hypertension inadequately controlled by medication, who were treated with renal denervation, there were sustained reductions in systolic blood pressure and fewer major cardiovascular events over 36 months of follow-up (J Am Coll Cardiol doi:10.1016/j.jacc.2022.08.802).

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**PACE labels**

Ten worksite cafeterias in England were randomised in the order in which they introduced labels containing information about physical activity calorie equivalents (PACE labels) on selected food and drinks. Judged by the primary outcome of total energy purchased each day, the intervention was ineffective. Although variation was seen between cafeterias, no consistent evidence showed that PACE labels influenced food choices (PLoS Med doi:10.1371/journal.pmed.1004116).

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**APOE4**

Inheriting a single copy of APOE4 raises the risk of developing Alzheimer’s disease around threefold, and having two copies increases the risk to eightfold. How this allele acts to cause brain damage has been something of a mystery. Experiments in transgenic mice and in cell culture now link the APOE gene with faulty lipid processing in oligodendrocytes. Cholesterol accumulates within the endoplasmic reticulum and myelination becomes defective (Nature doi:10.1038/s41586-022-05439-w).

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**Vascular risk factors and Alzheimer’s pathology**

On the subject of dementia, it’s well known that vascular factors strongly influence risk. One reason is that worsening cerebrovascular disease can lead to vascular dementia. But it also seems that vascular risk factors hasten the accumulation of Alzheimer’s disease pathology. In a longitudinal study from the Netherlands, hypertension, hypercholesterolaemia, and diabetes were associated with increased prevalence and severity of brain amyloid β deposition (measured by positron emission tomography) seven to 13 years later (Brain doi: 10.1093/brain/awac354).

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**Screening for diabetes**

Linking UK Biobank data to NHS data showed that, based on HbA1c concentrations at the time of enrolment, 1% of participants in the Biobank study who had undiagnosed diabetes. Further analysis found that the median time to clinical diagnosis for these people was 2.2 years. The investigators infer that a nationwide screening programme would identify undiagnosed cases of type 2 diabetes earlier and help people start treatment sooner. Mind you, there are no data about the potential harms of such a screening programme or about its cost effectiveness (Diabetologia doi:10.1007/s00125-022-05824-0).

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**Perception of flavour**

Taste is the sensation evoked when non-volatile substances stimulate receptors on the tongue. Flavour and smell sensations, in contrast, are produced when volatile compounds stimulate receptors in the olfactory mucosa of the nose. Although signals about both flavour and smell reach the brain through the olfactory nerve, the two are not the same. Smell is intelligence about the external environment while flavour is information about food in the mouth. The brain differentiates between the two by using cues such as sniffing, which signals smell, and taste, which signals flavour (inference-review.com/article/the-scent-of-flavour).

Cite this as: BMJ 2022;379:o2826