Inside: Mapping minds with machines: the promise and pitfalls of connectomic medicine

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What we carry forward: memory, medicine and change

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We would also like to thank the Deputy Vice Chancellor for Academic Affairs, Prof. Tracy Robson, for her sponsorship, and Margaret McCarthy in the DVCAA's office for her unwavering endorsement and assistance. Special thanks to Prof. Niamh Moran, Dr Shona Pfeiffer and Dr Aisling Heeran for their dedication, support and mentorship as the *Journal*'s academic advisors. A heartfelt thank you to the team at Think Media for seamlessly publishing the *RCSIsmj* to such a high standard year after year.

Cover art: *The House Call* by Maya O'Donnell
This piece is meant to highlight the dichotomy of tools and technology in medicine. The stage is set (literally) with the doctor's bag, something that has been used for centuries to deliver healthcare to patients during house calls. I wanted to emphasise such an approach to delivering healthcare, one where the doctor makes the trip, truly placing the patient's needs first. The contrast becomes evident as tools emerge from the doctor's bag illustrating the progression of medical devices from simple, handheld instruments to advanced technologies that require specialised expertise to operate. Specifically, I chose to incorporate robotic surgical arms to represent modern innovations that have significantly advanced surgical care by expanding minimally invasive procedures. These technologies allow for greater precision and improved surgical outcomes, once again placing patients at the forefront of care. As medical professionals continue to develop evidence-based discoveries and technologies, it is important to embrace innovation while also reflecting on the foundational practices that have shaped the field of medicine today.

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RCSIsmj contents

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A discipline in motion

Medicine is a profession built on memory. It carries forward the lessons of those who trained before us, the stories of patients who shaped our understanding, and the evidence base that continually defines our practice. Yet medicine is equally a discipline of change. Each generation inherits a system in motion and is asked not only to preserve its strengths, but to question its limitations. We move forward only by circling back, revising what once seemed certain, and accepting that progress is less a straight ascent than a winding, tangled journey towards an uncertain future.

This year's theme, 'What we carry forward: memory, medicine, and change', asks us to reflect on this challenge and to recognise ourselves within it. As medical students, we occupy a unique in-between moment. We are trained by traditions we did not create, preparing to enter a profession we will inevitably alter. The question is not whether change will occur, but what we choose to preserve as we pursue it.

Within this edition, you will find work that touches on this theme. This includes pieces that champion, but also astutely question, the ever-expanding role of technology in medicine, such as recent advances in robotic surgery, artificial intelligence-directed imaging, connectomics, and molecular wearables. These articles present technology as an exciting frontier, while emphasising our duty to be more purposeful in how we engage with it. In the narrative piece, 'The garden we carry', we are reminded that each patient arrives with a life already cultivated long before illness enters the room, and that the human connection is something that must be consciously preserved.

This issue also invites us to look thoughtfully at the systems we inherit. Articles exploring gender and reproductive health encourage us to consider where medicine has fallen short and how it can grow.

Similarly, this 19th edition owes much to its predecessors. The *RCSIsmj* organisation has been dutifully carried forward by a strong ethos of mentorship, collaboration, and a shared belief in leaving the *Journal* just a little bit better than we found it. Each edition represents an enormous collective effort from a community committed to lifting up and supporting the work of others. I am pleased to share the following collection. I hope it challenges you, inspires you, and reminds you of the profound responsibility and privilege that come with what we choose to carry forward.

Mitchell Neuert
Editor-in-Chief,
RCSIsmj 2025-2026

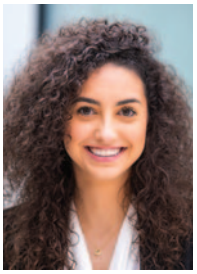
Defining what medicine will become

Medicine is a living discipline shaped across generations. It is carried forward through shared knowledge, lived experience, and the lessons we learn from patients who trust us with their lives. This 19th edition of the *RCSIsmj* reflects that continuity and responsibility. Under this year's theme, we are invited not only to consider what we inherit as future clinicians, but what we choose to carry forward, and what we choose to change.

This year has been one of meaningful growth for the *Journal*. We have expanded our platforms to further promote student writing and engagement, strengthened collaboration across campuses and disciplines, and continued to cultivate a publication that reflects the diversity, curiosity, and ambition of our student body. The *Journal* remains a space for first-time authors and emerging scholars, supported through mentorship and educational initiatives. In doing so, we ensure that this publication is not only a reflection of excellence, but also a tool for growth.

We remain committed to upholding the highest standards, refining our editorial processes, and ensuring that each edition reflects the quality and professionalism associated with RCSI on a global stage. This would not be possible without the support of many. I extend my sincere thanks to Think Media for their continued guidance throughout the publication process. Thank you to the Office of the Deputy Vice Chancellor for Academic Affairs, in particular Prof. Tracy Robson and Margaret McCarthy, for championing spaces that allow students to pursue curiosity beyond examinations. I am deeply grateful to Prof. Niamh Moran and our Academic Advisory Committee for their mentorship and support. To the *RCSIsmj* team – our student writers, editors, reviewers, and committees – your dedication and generosity are the foundation of our success.

The future of this *Journal* is something we continue to shape together. Each edition reflects students who are willing to think critically, write thoughtfully, and lead with integrity. If medicine is something we carry forward, then so too is this publication, evolving with purpose and sustained by those who choose to invest in it. In contributing to this *Journal*, we are not simply documenting medicine as it is; we are helping define what it will become.



Victoria Srbely
Director,
RCSIsmj 2025-2026

Ethics challenge 2026/2027

Advance directives and conflicting family expectations in the emergency department

Patricia Jennings (PJ), aged 75, with advancing dementia, is brought to the emergency department by ambulance from her home. Her eldest daughter, Jane, is her primary carer. PJ has developed pneumonia and is struggling to breathe. Her blood pressure is 90/60mmHg, raising concern for septic shock.

Jane has brought PJ's advance directive, which clearly states that no CPR should be performed if her heart stops. However, the directive does not explicitly mention other treatments such as antibiotics, intravenous fluids, or hospital admission.

During your initial assessment, PJ's other child, James, arrives. He insists that all treatments and interventions must be administered to his mother. Jane, the primary carer, maintains that PJ would prefer comfort care and minimal medical intervention.

You are the specialist registrar (SpR) on duty, but are unsure of how to proceed.

Questions to address:

1. How would you respect PJ's autonomy while ensuring that your approach is ethical and professional?
2 How can you manage or avoid conflict between her children while prioritising patient-centred care?
3. How can the four principles of medical ethics (autonomy, beneficence, non-maleficence, justice) guide your decision in a time-pressured emergency?
4. How would you resolve conflicts between these principles when they appear to contradict each other?

This is the 18th instalment of the *RCSIsmj* Ethics Challenge. The editorial staff would like to congratulate Andre Samir Ramkaran on his winning essay in the 2025/2026 Ethics Challenge. Please see page 6 for his submission.

We invite students to submit an essay discussing the ethical questions raised in the scenario presented. Medical ethics is an essential aspect of the medical curriculum, and we hope to encourage RCSI students to think critically about ethical situations that arise during their education and subsequent careers.

All essays will be reviewed by a faculty panel of experts, and the winning essay will be published in the 2027 print edition of the *RCSIsmj*. Please note that the deadline for submission will be available on our website – www.rcsismj.com – and will be separate from the general submission deadline for the 2027 edition of the *RCSIsmj*.

Submission guidelines

Please construct a lucid, structured, and well-presented discourse for the issues raised by this scenario. Please ensure that you have addressed all the questions highlighted, and discuss these ethical issues academically, making sure to reference when necessary. Your paper should not exceed 2,000 words.

Your essay will be evaluated on three major criteria:

1. Ability to identify the ethical issues raised.
2. Fluency of your arguments.
3. Academic quality with regard to depth of research, appropriateness of references, and quality of sources.

Good luck!

The winning entry will be presented with a prize at the launch of the next issue of the *RCSIsmj*.

ETHICS CHALLENGE WINNER 2025/2026

Navigating refusal, authenticity, and proportionate intervention in severe anorexia nervosa

Andre Samir Ramkaran
RCSI medical student

"To cure sometimes, to relieve often, to comfort always."

Anorexia nervosa (AN) is a disorder capable of remapping the very values that ordinarily guide medical choice. When a young adult refuses artificial nutrition and hydration (ANH) in an advance healthcare directive (AHD), and reiterates that refusal at a body mass index near 14, clinicians face an apparent collision: honour autonomy and risk a preventable death, or override refusal and risk violating the person's will. The easy slogans on either side – 'respect choice' or 'save life' – fail to capture how AN distorts judgement about food, weight, and self-worth; nor do they account for the law's simultaneous commitment to respecting will and preferences while safeguarding life in emergencies. This essay argues for a principled middle course: a relational-autonomy stance married to proportionate, time-limited intervention. Relational autonomy recognises that agency is scaffolded by relationships, information, and viable alternatives, not exercised in isolation. Proportionate intervention holds the line against avoidable death while refusing to allow compulsion to become a default or an indefinite project. Drawing on Irish consent law, the Assisted Decision-Making (Capacity) Act 2015, the interface with the Mental Health Act 2001, and contemporary clinical guidance for medical emergencies in eating disorders, this essay aims to articulate a framework that is both humane and legally coherent. Within this framework, refusals that are authentically and lawfully made warrant respect, intervention is justified when risk is extreme and benefit remains plausible, and treatment should stop when it imposes burden and no benefit.

Autonomy, authenticity, and the anorexic lens

Autonomy in healthcare is decision and time specific, not a blanket attribute one either possesses or lacks. In AN, patients may present with intact *procedural* abilities, such as understanding, retaining, reasoning, and communicating, while the *content* of their values around weight restoration, risk appraisal, and self-worth has been

reshaped by the illness. The familiar capacity questions, 'Do you understand?', and 'Can you weigh the options?', can be answered correctly, while the priorities that drive the decision are captured by the disorder's logic: thinness as safety, calories as threat, physiological collapse as less terrifying than weight gain. The literature on decision-making in AN shows precisely this tension, demonstrating that formally competent thinking processes alongside illness-shaped values can pull decisional content towards self-harmful choices.[1-3] The ethical mistake is to treat autonomy as a checklist that ends at the surface of the test. What matters is whether a refusal reflects the recognisable continuity of the person's values or a value set so colonised by illness that the refusal no longer carries the authority of the self we hope to respect.

Taking authenticity seriously does not license paternalism. It redirects respect away from a thin, checkbox version of autonomy towards a richer commitment to the patient as a continuing subject of value. Practically, that means offering supports that widen the space for genuine choice, including protective relationships, risk information delivered in tolerable doses, behavioural strategies to reduce postprandial distress and, with consent, the involvement of those the patient trusts. Respect in this sense is not passive. It is an active attempt to make the least restrictive option workable and to see whether, with anxiety contained and supports in place, a capacitated decision emerges that clinicians can confidently honour.

Autonomy deserves respect; authentic autonomy demands scrutiny

This perspective clarifies the first fork in Jenny's road. If, after generous support, she demonstrates current capacity to refuse ANH, then the contemporaneous decision holds. If she lacks capacity and a valid, applicable AHD explicitly refuses life-sustaining ANH, the default position in general medical care is to respect it. Neither outcome amounts to abandonment. In both scenarios, clinicians remain bound to relieve suffering and to comfort, even as they refrain from treatment the patient rejects. The harder cases arise where capacity is doubtful, the AHD is unclear, or the refusal seems to speak more for the illness than for the person. There, ethics does not yet decide *what* to do; it decides *how* to decide – that is, slowly, supportively, and with an eye for authenticity.

Advance directives and Irish law: when refusal binds, and when it does not

Irish law begins with a presumption of capacity and imposes duties to support decision-making: a framework that is operationalised across health services through the HSE's National Consent Policy.[4] The Assisted Decision-Making (Capacity) Act 2015 gives legal effect to AHDs. A valid and applicable AHD refusing life-sustaining treatment, including ANH, must be respected if the directive explicitly covers it and the person lacks capacity at the time the AHD is to operate.[5,6] Two questions dominate the legal terrain in cases like Jenny's. The first concerns validity, namely whether the directive was properly executed, witnessed, and not revoked. The second concerns applicability, meaning whether the present clinical circumstances match those the directive anticipated, and whether it expressly covers ANH as life-sustaining treatment.

The crucial wrinkle is the interface with the Mental Health Act 2001. Where statutory criteria for involuntary admission and treatment are met, Part 4 powers can authorise treatment without consent when necessary to safeguard life or prevent serious deterioration.[7] In that setting, a previously valid directive may not control decisions taken under the Act's regime. However, nothing in the statute makes compulsion easy. Necessity and proportionality remain hard limits: treatment should be the minimum required, for the shortest feasible time, and subject to regular review. These legal rails do not replace ethics; they house it by providing authority for urgent intervention where needed, and insisting that such authority be exercised narrowly and with accountability.

Clinical risk and proportionality: MEED as the safety compass

Ethical argument drifts without a clinical compass. The Royal College of Psychiatrists' Medical Emergencies in Eating Disorders (MEED) guidance (CR233) provides one. It asks teams to characterise physiological risk explicitly, using electrolytes, electrocardiography, haemodynamic stability, glycaemic control, and organ compromise, rather than treating "BMI alone", and to choose the least restrictive plan that can actually avert foreseeable harm.[8,9] Within that logic, a time-limited, goal-directed trial of treatment has ethical traction when there is a plausible prospect of benefit. A reasonable ladder runs from collaborative oral nutrition with intensive support to short-term nasogastric feeding without restraint, to nasogastric feeding with minimal restraint and, only in exceptional circumstances, to sedation-assisted feeding. Each rung requires explicit goals, frequent review, and off-ramps; if the targets are not met or the burdens, such as restraint, sedation and complications, mount, the justification collapses. Proportionality is not a slogan but a structure. It asks first whether any intervention is necessary to prevent a serious, near-term harm; then, which intervention can achieve that aim at the lowest cost to rights and dignity; and then,

how long such measures can ethically continue before they become a project of suffering rather than a bridge to recovery. When a trial shows that physiology stabilises, medical risk recedes, and engagement becomes possible, a short period of temporary compulsion can be justified. When, despite best efforts, nutrition cannot be established without repeated restraint and escalating sedation, and when organ failure or refractory psychological distress dominates the picture, proportionality counsels stopping.

Jurisprudence at the edges: what best interests really ask

Though not binding in Ireland, recent UK Court of Protection decisions illuminate how person-centred best interests work at this edge. In *Re E*, the court authorised feeding where capacity was lacking and prospects of benefit were credible. In *Northamptonshire v AB* and *Re Patricia*, by contrast, the courts concluded that further forced feeding, given cumulative burdens and bleak outlook, was not in the person's best interests, and endorsed a shift towards comfort-focused care.[10-12] The Supreme Court's articulation in *Aintree v James* remains compelling. Best interests are not the clinician's conception of 'best medicine', but the course that accords with the person's perspective: their values, wishes, and sense of what a life worth living would require.[13] These decisions do not supply a single answer for all cases; they supply a method. Where life-sustaining treatment offers a real prospect of reopening a future the person could value, escalation can be justified despite present refusal. Where treatment would impose only burden and no meaningful future benefit, courts have been prepared to say 'no more'. The force of that jurisprudence is not its jurisdictional reach but its moral grammar, which includes person-centred ends, proportionate means, and continuous review.

When treatment becomes all burden and no future, compassion changes course.

Applying the framework to Jenny

Jenny is 23. She states that she would rather die than be force-fed, refuses ANH in an AHD, and presents with signs consistent with severe medical risk. How should a conscientious team proceed?

First, assess capacity here and now for the specific decision about ANH. The evaluation must be disorder sensitive. Does Jenny not only understand the medical information, but appreciate what it means for her, including the short-term risks of refeeding versus near-term risks of arrhythmia, heart failure, or irreversible organ injury? Can she weigh these factors in a way that is not wholly captured by the illness's narrowed values? Has she shown a stable, considered preference over time, or are there flickers of alternative values? The reasoning should be carefully documented, include senior psychiatry input, and, at her request, involve trusted supporters. If, after generous support, she has capacity and refuses ANH, that contemporaneous decision should be respected.

Second, examine the AHD's validity and applicability. Is the refusal explicit about life-sustaining treatment and ANH? Was it made when she demonstrably had capacity? Do the present circumstances match those the directive anticipated? If she currently lacks capacity and the directive is both valid and applicable, then, absent mental health detention, the refusal should be honoured. Respect here does not mean retreat. It means a pivot to comfort-focused care and meticulous attention to symptom control, dignity, and distress, with the same professional seriousness one would bring to a decision to forgo ventilation in another illness.

Third, if capacity is absent and the directive is invalid or inapplicable, consider a time-limited, least-restrictive trial, because risk is high and benefit plausible. The therapeutic intent and limits should be stated in advance, including initial caloric targets, correction of electrolyte disturbance, clear metrics for responsiveness, and an agreed stopping rule if goals are not met. Document why this plan is proportionate now and how it will be reversed if the burdens mount without physiological or psychological improvement. The aim is not to conquer the patient but to buy time for medical stabilisation and for the re-emergence of a decision that might again be authentically hers.

Fourth, if collaborative measures fail and statutory criteria for involuntary treatment are met, seek legal advice and, where appropriate, court oversight, for short, reviewable authorisations. Emphasise necessity and proportionality, involve an ethics service, and build in explicit review dates. The point of court involvement is not to outsource moral judgement but to safeguard rights when coercion is contemplated, and to provide a neutral forum for genuine disputes about capacity, directive applicability, and proportionality. Where a court does authorise feeding, the authorisation should be tightly bound with explicit goals and review points – a standing licence to compel is neither ethically nor legally defensible.

Finally, recognise the point at which further escalation is non-beneficial. That point is reached when realistic prospects of recovery are minimal, when burdens – repeated restraint, escalating sedation, complications signalling organ failure – dominate the clinical picture, and when the life on offer no longer matches what the person could reasonably value. At that point, the humane path is a palliative pivot, not a louder insistence on technical possibility. To comfort always is not to surrender; it is to accept that compassion sometimes refuses further harm even when intervention remains possible.

Two live debates worth addressing

"Terminal anorexia"

Recent proposals to recognise a category of "terminal AN" purport to legitimise refusal and, in some jurisdictions, raise questions about assisted dying. The label overstates prognostic certainty by analogising to metastatic cancer and risks short-circuiting careful capacity, applicability, and proportionality analysis. Jenny's case should be resolved by those tools, not by a contested label.[14]

Does compulsion work?

Rapid reviews suggest that compulsory treatment can be life-saving, but carries significant therapeutic and personal costs, with uncertain predictors of who benefits. This finding supports a conservative threshold for compulsion and strong safeguards when it is used.[15]

Conclusion

Cases like Jenny's do not ask us to choose between autonomy and beneficence; they ask us to protect authentic autonomy while preventing avoidable death. A relational-autonomy stance, coupled with proportionate, time-limited intervention, reconciles Irish consent law, mental health powers, and the clinical realities of medical emergencies in eating disorders. The course is disciplined but not rigid. Respect refusals that are valid and authentic. Intervene when risk is extreme and improvement plausible, with clear goals and strict ceilings. Stop when treatment becomes all burden and no future, and let the law enable and review that decision rather than dictate it in the abstract. In Jenny's case, this framework supports honouring a capacitated contemporaneous refusal or a valid, applicable directive outside the mental health regime. It permits short, tightly reviewed authorisation for feeding only where MEED-level risk is imminent and collaborative options have failed, and it accepts a palliative path when further life-prolonging attempts are no longer in her interest. This is not fence-sitting. It is the discipline of medicine at its best: principled, humane, and exacting.

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Don't take yourself too seriously – take your work seriously

Student Staff Writer SAGAR KOTHARI spoke to Dr Joseph Kim about what medical students should consider as they prepare for the future of the profession.

Dr Joseph Kim, transplant nephrologist, University Health Network, Canada.

Dr Joseph Kim is a transplant nephrologist at the University Health Network, Canada, and a Professor of Medicine at the University of Toronto. In addition to his clinical work in kidney transplantation, he is a physician scientist with advanced training in epidemiology, statistics, and health systems leadership. His career spans clinical medicine, research, education, and health system governance, offering a uniquely holistic perspective on modern medical practice.

Can you tell us about your experience at medical school and how you found your way into nephrology and transplantation?

I went to the University of Toronto for medical school, an internal medicine residency, and a nephrology and kidney transplantation fellowship. During the summer between first and second year of medical school, I worked on a research project at St. Michael's Hospital in Toronto with Dr Jeffrey Zaltzman, who was the director of kidney transplantation at the time. That experience really shaped my thinking. He made a very compelling case to pursue a career in transplantation. I remember him saying: "There are only two reasons to ever be happy to come to the hospital: one is to deliver a baby, and the other is to get a transplant". That stuck with me. I also found nephrology intellectually satisfying. An abnormal creatinine was fascinating to me in that it was like a diagnostic puzzle. It was objective and measurable. Transplantation added another layer: the science, the immunology, the human leukocyte antigen (HLA) matching, and the fact that the distance between laboratory discovery and clinical application was relatively short compared to other fields. That combination was very attractive.

How did your education evolve after residency?

After residency, I went to Johns Hopkins in Baltimore to pursue a research career at a top institution. I completed a PhD in epidemiology and a master's in statistics. It was challenging, as I didn't come from a strong mathematical background, but it became one of the best decisions I made. That training distinguished me when I returned and shaped my career as a physician-researcher and educator. If you pursue advanced training, think about what interests you and how you can add value as that's what makes people seek you out.

Were there defining moments or mentors that shaped how you practise medicine today?

Meeting Dr Zaltzman was certainly one of them. Another defining influence was Dr Carl Cardella, who was exceptional at asking questions. He emphasised thinking critically about evidence and recognising that the evidence base behind many of our practices isn't as solid as we might assume. That realisation pushed me toward

research. Either you can accept the uncertainty you deal with, or you can be part of the solution and improve the evidence.

Individual patients also played a big role. I remember a case involving an elderly woman with a very large, involved family. There were tensions among family members, people flying in, and many voices trying to direct care. That experience taught me that, while the patient must always come first, family dynamics matter enormously. It forced me to think holistically while keeping a clear focus on what truly mattered for the patient.

Does engaging in research make someone a better clinician?

I think research itself is valuable, but the bigger benefit is learning to think scientifically. Conducting a project from start to finish teaches you how to ask questions, evaluate evidence, and seek answers critically. Those skills extend far beyond research. Even if someone doesn't pursue it as a career, that way of thinking is essential for good clinical practice. Medicine demands objectivity, and research can help develop that mindset. The value of research goes way beyond research; it teaches you how to think. And it's fun! It's social, collaborative, and has the potential to change lives.

You've spoken a lot about balance, priorities, and self-care. How did those lessons develop over time?

I learned many of these lessons later than I wish I had. Early in my career, I focused almost exclusively on academics. I didn't take good care of myself: I ate poorly, didn't exercise, and my health suffered. We talk about balance all the time, but balance doesn't mean the fulcrum is always in the middle. It's dynamic. At different stages of life, priorities shift. You must be deliberate about that and accept that sometimes it means missing a conference to attend a piano recital. Those decisions define who you are, not as an academic, but as a person. At the end of the day, the people who will remember me when I'm retired are my family. That perspective matters. Don't take yourself too seriously, but take your work seriously.

You've also spoken about being deliberate in your decisions. When did that become important to you?

Probably later than it should have. I don't regret my choices, but what I came to appreciate over time is that career progression doesn't just happen by accident. You're always making choices, whether you acknowledge them or not. You need some sense of what you're trying to build toward over the next five or 10 years … not a job title, but why you're doing what you're doing.

Being deliberate means thinking not just about what you're going to do, but what you're not going to do. Every yes implies a no somewhere else. If you don't actively decide, those trade-offs still happen – they're just made passively. That applies to research projects, leadership roles, and especially to life outside of work. If something matters to you, whether it be family, health, relationships, etc., you must protect it intentionally. It won't protect itself.

How did your interest in leadership and pursuing a Master of Business Administration (MBA) come about?

I started thinking about an MBA after becoming director of the kidney transplant programme. I realised that being a good clinician or researcher didn't automatically translate into being a good leader. Leadership requires a different skill set.

I pursued an MBA at the University of Toronto with colleagues, and it was transformative. It helped me think strategically about healthcare systems, quality, safety, and how to mobilise people around a shared vision. Leadership is less about doing everything yourself and more about empowering others. That's something I'm still working on.

Looking ahead, what should medical students understand about the future of medicine, especially with artificial intelligence (AI) and data?

The core of medicine (i.e., diagnosis, prognosis, and management) remains the same. What's changing are the tools. AI is fundamentally a prediction machine, and much of what we do cognitively is prediction. Its impact will be profound.

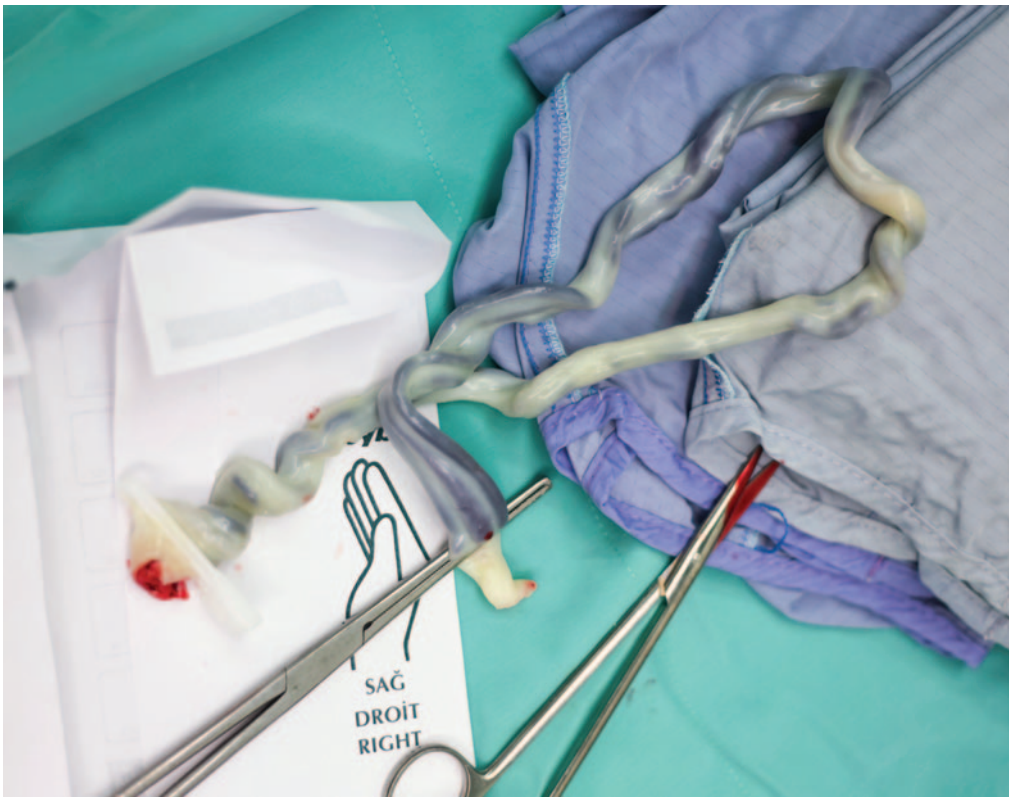
Medical students don't need to learn how to code, but they should understand concepts like machine learning and large language models. Physicians must remain central in providing context and meaning to data. If we don't actively engage with these changes, they will happen without us.

Finally, is there anything you wish you had known as a student?

Honestly, I wouldn't change my trajectory. I've enjoyed how things unfolded. The one thing I do regret is not protecting my health earlier. Self-care is a deliberate choice, and I wish I had made it sooner.

Finally, the practice of medicine remains one of the most important roles in society. Being a healer is a calling. But physicians must now think beyond individual patients – to populations, systems, and policies. Students today are in a powerful position to help shape that future.

Delayed versus early cord clamping and iron status in infants



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Declaration of generative AI
During the preparation of this manuscript, the author(s) used generative artificial intelligence (GenAI) to assist, where applicable, with language editing, sentence refinement, and improvement of readability. All content generated or modified using these tools was carefully reviewed and verified by the author, who takes full responsibility for the integrity, accuracy, and originality of the work.

Abstract

Umbilical cord clamping is a routine practice in obstetrics with significant implications for neonatal well-being. Early cord clamping (ECC), performed within the first minute after birth, has previously been the standard approach. In contrast, delayed cord clamping (DCC), performed after one minute, has gained prominence for its neonatal benefits – most notably, increasing infant iron stores and potentially reducing iron deficiency and neurodevelopmental conditions. This review compares ECC and DCC, with a focus on infant iron stores, and differences in maternal and neonatal outcomes. Evidence suggests that DCC increases iron stores for up to eight months, lowering the risk of iron deficiency and its sequelae. While DCC has been associated with increases in polycythaemia and jaundice, these conditions are generally mild and easily managed. Maternal outcomes, including postpartum haemorrhage (PPH), haemoglobin levels (Hb), and transfusion rates show no significant difference between ECC and DCC. Future research should address the lack of long-term research (greater than 12 months), poor DCC guidelines, and scarcity of research conducted in low-resource settings to ensure that the benefits of DCC can be achieved globally.

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Introduction

Cord clamping is a critical component of the third stage of labour. It refers to clamping and cutting the umbilical cord after placental pulsation has ceased but before placental delivery. There are two types of clamping: early cord clamping (ECC), which is performed within one minute of birth; and, delayed cord clamping (DCC), performed after one minute.[1] Cord clamping was first described in the 17th century, when the umbilical cord was tied and cut before placental delivery – marking a shift from earlier practices in which the cord was usually cut only after placental expulsion.[2,3] At the time, clamping was thought to prevent neonatal blood loss before spontaneous vessel closure, though some argued that it deprived infants of vital blood. In the early 20th century, the discovery of the umbilical cord as a source of transfusion blood further increased the practice of clamping the cord before placental delivery due to its distinctive immunological and haematopoietic properties.[3]

Modern obstetric practice manages the third stage of pregnancy in two ways: physiological or active. Physiological management uses DCC and allows the placenta to be expelled by maternal contractions. Active management includes prophylactic uterotonic administration and ECC, a practice that became the norm since it was believed to lower the risk of postpartum haemorrhage (PPH).[3] The proposed benefits of ECC include quick neonatal removal from the operating field so that the surgeon can focus on completing the surgery and achieving haemostasis. Also, neonatal respiratory depression is a major complication of opiates and general anaesthesia; thus, the shorter duration of ECC may reduce the time needed for neonatal resuscitation.[3] Historically, maternal apnoea and procedural convenience also often supported early clamping.[4] Although many benefits have been reported, recent meta-analyses have shown that clamping time did not affect the PPH risk, due to no differences in mean blood loss or maternal haemoglobin (Hb) levels.[5-7]

Cord clamping is a critical component of the third stage of labour. It refers to clamping and cutting the umbilical cord after placental pulsation has ceased but before placental delivery.

In recent years, DCC has gained prominence in clinical guidelines because of its neonatal benefits. The timing of cord clamping determines the volume of placental blood and iron transferred, making this simple intervention highly consequential for infant health.[6,8] In infants, iron deficiency (ID) is defined as a ferritin of less than 12mg/L.[8] By allowing greater placental transfusion, DCC may improve neonatal iron stores and reduce the risk of iron deficiency (ID) – the most common nutritional deficiency worldwide, affecting nearly 42% of children under five years, and a major contributor to impaired neurodevelopment.[9,10] Despite significant strides in cord clamping research, some contention remains regarding long-term effects on neonatal iron stores, and maternal and neonatal outcomes. This review will evaluate whether ECC or DCC is more beneficial for neonatal iron stores. This will be done by exploring the physiology of iron transfer and the consequences of each clamping type on iron stores, and maternal and neonatal outcomes. Then, it will highlight the gaps in research concerning standardising protocols, refining guidelines, increasing research on long-term outcomes, and focusing on research in low-resource populations.

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Physiology of iron transfer

The placenta, a temporary organ of pregnancy, plays a crucial role in the transfer of iron to the foetus. Iron is transported from the maternal circulation across syncytiotrophoblasts (STBs) into the placenta in a unidirectional manner.[11] Circulating as diferric transferrin, maternal iron binds to transferrin receptor 1 on STBs and is internalised. Within the STB, iron undergoes numerous changes and is stored within the cytosol. When needed, iron is utilised by the placenta or exported to the foetus via ferroportin (FPN1), a transporter found on the basolateral membrane of the STBs, which is the foetal-facing side of the placenta.[11] Alternative pathways on the foetal endothelium, such as transferrin receptors, support foetal iron delivery due to the lack of FPN1 in the foetal endothelium.[11] When there are insufficient iron reserves, the placenta will prioritise its own iron requirements at the expense of foetal reserves, a concept known as the "selfish placenta".[11] Other than facilitating blood oxygen-carrying capacity, iron is crucial for brain growth, myelination, and neurotransmitter/energy production. Neonatal ID can impair neurodevelopment, which manifests as low attention scores, impaired sleeping patterns, poor recognition and memory, and disrupted motor development.[5,12] Conversely, iron overload has also been shown in murine models to cause neurodevelopmental effects and may underlie diseases such as

Alzheimer's and Parkinson's disease.[13] This further supports the idea that iron optimisation is essential during pregnancy, and that the timing of cord clamping may aid in preventing extreme deviations in iron stores.

The transfer of blood from the placenta to the newborn within the first minute of life is around 80mL and increases to 100mL within the first three minutes. This process is facilitated by the infant's initial breaths and is enhanced by DCC. The additional blood transported to the newborn supplies around 75mg of iron, which has been shown to reduce the risk of ID and neurodevelopmental conditions.[5,7,8,14]

Consequences of early versus delayed cord clamping

ECC has historically been the standard; however, recent research has advocated a shift towards delayed clamping.[5] Traditionally, ECC was applied routinely during childbirth, yet evidence now supports DCC to improve neonatal outcomes. Some benefits include lower rates of anaemia (19.3% vs 33.3%) and lower rates of necrotising enterocolitis.[5,8,15] A Cochrane review analysed 15 studies containing 2,333 babies and concluded that DCC is associated with a reduced risk of intraventricular haemorrhages.[15] However, this is not without consequence, since multiple studies report slight increases in bilirubin and subsequent jaundice, with rates of approximately 2.74% in ECC infants compared to 4.36% in DCC infants, alongside cases of polycythaemia.[3,5,7] In contrast, ECC newborns avoid these complications, but forego the benefits of higher Hb and iron stores, which are beneficial for neurodevelopment.[10] Fortunately, if equipped with adequate resources, jaundice and polycythaemia are typically manageable and do not pose significant harm to the well-being of the infant.[5]

As research on DCC has expanded, varying recommendations on the optimal duration before clamping have emerged. **Table 1** provides an overview of the current international recommendations on umbilical cord clamping times.

Despite these recommendations, barriers such as entrenched tradition, difficulty in implementation, lack of knowledge, and guidelines prevent DCC from being the primary method of cord clamping after birth.[3,16] There is broad consensus that DCC should be performed and standardised in practice, but clear, concise protocols are needed to ensure that all health professionals can implement it safely and effectively.[5]

Impact of clamping on iron stores

ID is the most common nutritional deficiency in children, affecting approximately 42% of children under five years.[9] Research has increasingly shown that DCC improves infant iron stores during the early months of life compared to ECC.[1,8,14,17,18] At birth, infants in both groups have similar iron stores (9.9µmol/L) and comparable ferritin levels (300µg/L vs 312µg/L).[14] However, differences emerge over time. A randomised controlled trial by Anderrson *et al.* (2011) demonstrated that DCC (>180 seconds post birth), when compared to ECC (<10 seconds post birth), increased infant ferritin levels (117µg/L vs 81µg/L) and reduced ID prevalence (0.6% vs 5.7%) at four months.[14] Other studies support these findings: Chopra *et al.* (DCC: 86ng/mL vs ECC: 50.5ng/mL), and Gupta *et al.* (DCC: 118.4µg/L vs ECC: 73µg/L) reported higher iron levels in DCC infants at three months, while Chaparro *et al.* reported similar findings at six months (DCC: 50.7µg/L vs ECC: 34.4µg/L).[1,18,19]

Table 1: Current recommendations on umbilical cord clamping times.[5]

Organisation	Recommended timing
World Health Organization (WHO)	Delay clamping for more than one minute.
American Academy of Pediatrics (AAP)	Delay clamping for 30-60 seconds.
Royal College of Obstetricians and Gynaecologists (RCOG)	Delay clamping for more than two minutes.
American College of Nurse-Midwives (ACNM)	Delay clamping for two to five minutes.

Barriers such as entrenched tradition, difficulty in implementation, lack of knowledge, and guidelines prevent DCC from being the primary method of cord clamping after birth.

The evidence is less concordant when comparing older infants. A subsequent trial conducted by Anderrson *et al.* (2017) examined the eight- to twelve-month age group. While DCC was found to increase iron stores for eight-month-olds (DCC: 21.8µg/L vs ECC: 16.4µg/L, p<0.001), no significant effects were observed on infants at 12 months (DCC: 15.6µg/L vs ECC: 13.2µg/L, p=0.14).[8] These results are consistent with those reported in an earlier study by Andersson *et al.* (2014), which also concluded that DCC did not affect iron status or neurodevelopment at 12 months of age based on the Ages and Stages Questionnaire (ASQ) focusing on communication, fine motor, gross motor, personal-social and problem solving skills.[17] Nonetheless, Hb levels remained higher and anaemia rates lower in infants between the ages of eight and twelve months in the DCC group.[8] The decreased benefit from DCC in later months has been attributed to the introduction of solid foods, specifically iron-fortified foods, which

decreased the difference in iron stores between ECC and DCC infants.[8] This suggests that while DCC helps to reduce the risk of early ID in infants, the development of ID after eight months is likely influenced by factors beyond whether ECC or DCC was used.

There is broad consensus that DCC should be performed and standardised in practice, but clear, concise protocols are needed to ensure that all health professionals can implement it safely and effectively.

Effects of cord clamping on maternal and neonatal outcomes

Of all the potential benefits of ECC, evidence of it enabling a faster resuscitation time remains inconsistent; multiple research articles report no significant delay in resuscitation with DCC.[6,20] Katheria *et al.*[21] conducted a randomised clinical trial evaluating resuscitation with an intact umbilical cord compared to immediate clamping in preterm infants. The results found no significant difference in delivery room interventions. Oxygen saturation, time to ventilate, and stable heart rate were similar between the two groups, suggesting that intact cord did not delay neonatal resuscitation.[21]

The decreased benefit from DCC in later months has been attributed to the introduction of solid foods, specifically iron-fortified foods, which decreased the difference in iron stores between ECC and DCC infants.

Although the timing of cord clamping may not greatly impact the mother, some claims must be addressed. Some previous studies have suggested that mothers who undergo ECC are more likely to suffer from PPH.[22] This proposition manifests from the idea that with early cord clamping, a larger amount of blood remains in the placenta. When combined with immediate uterine massage and cord traction on an overly full placenta and exhausted uterine muscles, it may increase the risk of PPH.[22] However, the majority of evidence indicates that there is no significant difference in PPH incidence between both types of clamping.[5,6] Similarly, maternal Hb, blood loss, and transfusion rates do not differ significantly between ECC and DCC. Finally, although ECC may shorten the duration of the third stage of labour, DCC does not drastically lengthen it.[6] For example, a randomised clinical trial reported that the average duration for a scheduled term caesarean section was 58 minutes for DCC and 54 minutes for ECC, with no statistically significant difference.[23] Ruangkit *et al.* similarly concluded that there were no significant differences in operative time between ECC and DCC (35.3±18.2 vs 37.4±13.2 minutes), reinforcing that the duration of labour is largely determined by individual circumstances such as parity and epidural anaesthesia use.[6,24,25]

Overall, evidence suggests that maternal outcomes do not differ substantially between ECC and DCC. Given the clear neonatal advantages, DCC should be implemented and regarded as best practice in routine childbirth.

Conclusion

The debate around ECC and DCC has been discussed since the 17th century; however, the consensus supports DCC as the standard approach for most births. Most notably, DCC increases infant iron stores for up to eight months, reducing the risk of ID that is typically seen in infants around six months. By lowering ID, DCC contributes to improved neurodevelopment of the infant. Although DCC is associated with polycythaemia and jaundice, these conditions are both easily treatable and should not deter the use of DCC.

Maternal outcomes show minimal differences between ECC and DCC, while increased Hb and iron stores support the superior neonatal benefits of DCC.

Several limitations remain in the literature. Guidelines for cord clamping vary widely, particularly regarding the optimal timing and reference ranges for ID in infants. Future research should focus on standardising protocols, investigating long-term outcomes (beyond 12 months) of the increased iron stores in infants who underwent DCC, and more closely monitoring maternal outcomes such as PPH in high-risk groups. Finally, there is a pronounced lack of evidence from low-resource settings where the rates of ID and anaemia tend to be highest. Since DCC comes at no additional cost, implementing DCC in low-resource settings could potentially decrease infant mortality and ID without requiring expensive technology and medications. Investment in research in low-resource settings would greatly benefit these populations and transform policies to improve neonatal outcomes.

Maternal outcomes show minimal differences between ECC and DCC, while increased Hb and iron stores support the superior neonatal benefits of DCC.

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Menstrual blood-derived stem cells in endometrial regeneration

Abstract

Endometrial damage remains a major cause of infertility, recurrent pregnancy loss, and menstrual dysfunction. Current treatments, including surgical adhesiolysis and hormonal therapy, frequently fail to restore complete endometrial function, leaving a critical gap in effective therapeutic options. Regenerative medicine has emerged as a promising strategy, with menstrual blood-derived stem cells (MenSCs) offering unique advantages. MenSCs can be harvested non-invasively and repeatedly, exhibit rapid proliferation, and share close phenotypic and functional similarities with native endometrial stromal cells. Preclinical studies demonstrate that MenSCs enhance endometrial repair through paracrine signalling, angiogenesis, anti-fibrotic effects, and immunomodulation, leading to improvements in structure, vascularisation, and implantation-related molecular markers. Animal models consistently show restored endometrial thickness, glandular density, and fertility outcomes following MenSC therapy, particularly when combined with biomaterial scaffolds. Despite these advances, clinical translation is still in its infancy. Challenges include heterogeneity in cell populations, lack of standardised isolation and characterisation protocols, manufacturing and scale-up barriers, and the need for rigorous safety and long-term monitoring. Addressing these limitations through well-designed clinical trials, consensus definitions, and optimised delivery systems is essential. MenSC-based therapies hold significant potential to revolutionise the management of endometrial disorders, offering novel, effective, and patient-friendly solutions to conditions that currently lack curative treatments.

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Declaration of generative AI

During the preparation of this manuscript, the author(s) used generative artificial intelligence (GenAI) to assist, where applicable, with language editing, sentence refinement, and improvement of readability. All content generated or modified using these tools was carefully reviewed and verified by the author, who takes full responsibility for the integrity, accuracy, and originality of the work.

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Introduction

Endometrial damage is a significant clinical challenge affecting millions of people worldwide. Asherman's syndrome, characterised by intrauterine adhesions (IUAs), affects up to 1.5% of women evaluated for infertility and 5-39% of those with recurrent pregnancy loss.[1] Even after surgical adhesiolysis, endometrial function often remains impaired, contributing to reduced fertility outcomes.[1]

Although surgical adhesiolysis can restore the uterine cavity in women with IUAs, residual endometrial dysfunction often persists, leading to higher risks of adverse obstetric outcomes such as preterm delivery and abnormal placentation.[2] Despite surgical adhesiolysis, reproductive outcomes remain poor for many women with IUAs, with only 46.9% achieving live birth following treatment.[3] This therapeutic gap leaves many women with poor reproductive outcomes and limited curative options.

Regenerative medicine offers the potential to rebuild functional endometrial tissue through stem cell-based interventions. Among various stem cell sources investigated, menstrual blood-derived stem cells (MenSCs) have garnered particular attention due to their unique advantages for gynaecological applications.

MenSCs are naturally shed during each menstrual cycle and can be harvested non-invasively in substantial quantities using simple collection methods.[4,5] This accessibility makes them a practical autologous cell source that can be obtained repeatedly without the ethical concerns or technical challenges associated with other stem cell types.[5]

MenSCs are particularly compelling due to their intrinsic relationship to endometrial tissue. These cells are morphologically and functionally similar to endometrial stromal cells, expressing both mesenchymal stem cell (MSC) markers and embryonic stem cell markers – a dual phenotype that reflects their exceptional regenerative potential.[5,6] Their rapid proliferation capacity, combined with renewable collection, creates an abundant source for therapeutic applications, positioning MenSCs as uniquely suited for uterine regenerative medicine.[7]

Biological characteristics and properties

MenSCs represent a distinct population of mesenchymal-like stem cells isolated from menstrual fluid through simple, non-invasive collection methods.[4] The isolation process involves processing menstrual blood within hours of collection, followed by density gradient centrifugation and selective cell culture techniques.[4]

MenSCs exhibit typical MSC traits and unique features. They adhere to plastic, express MSC markers (CD73, CD90, CD105), and lack haematopoietic markers (CD45, CD34).[5] Unlike conventional MSCs, MenSCs also express pluripotency markers (Oct-4, Sox-2, Nanog), supporting enhanced differentiation and regenerative potential.[8] They proliferate faster than bone marrow MSCs, doubling every one to two days, and maintain clonogenicity across passages, demonstrating superior expandability and therapeutic promise.[7,9]

The differentiation potential of MenSCs extends beyond traditional mesodermal lineages. Under appropriate culture conditions, research has demonstrated their ability to differentiate into multiple cell types including hepatocytes, neurons, osteoblasts, chondrocytes, adipocytes, endotheliocytes, cardiac myocytes, pulmonary epithelial cells, insulin-producing cells, and ovarian-like cells.[9]

Beyond their stemness properties, MenSCs possess functionally important capabilities that enhance their regenerative utility. They constitutively secrete diverse bioactive factors including growth factors, cytokines, and extracellular vesicles that influence surrounding tissues.[10] Most notably, they exhibit pronounced immunomodulatory and anti-inflammatory properties that may exceed those of other endometrial MSCs.[11]

Comprehensive studies demonstrate that MenSCs effectively suppress T cell proliferation through both contact-dependent and soluble factor-mediated mechanisms, while modulating cytokine profiles.[12] They consistently upregulate anti-inflammatory factors like interleukin 10 (IL-10) and transforming growth factor-β (TGF-β), while downregulating pro-inflammatory mediators such as interferon-γ (IFN-γ), tumour necrosis factor alpha (TNF-α), and IL-1β.[12,13] These immunoregulatory effects help protect engrafted cells from immune rejection, reduce local inflammation, and create favourable microenvironments for tissue regeneration.[13,14]

Preclinical evidence for endometrial repair

Animal studies have provided compelling proof-of-concept evidence for MenSCs' therapeutic efficacy in endometrial regeneration.[15] These studies utilised well-established rodent models that closely replicate human endometrial disorders, providing valuable insights into therapeutic mechanisms.

Rodent models of IUAs, which mimic Asherman's syndrome pathophysiology, have consistently demonstrated significant improvements following MenSC transplantation.[16,17] These models involve mechanical or chemical endometrial injury followed by assessment of adhesion formation, endometrial thickness, and fertility outcomes.

In a 2024 study by Wu *et al.*, MenSCs delivered via a gelatin-based hydrogel (VitroGel) produced dramatic improvements in rat IUA models.[16] The combination therapy substantially reduced fibrotic

adhesion formation and chronic inflammation, while achieving partial fertility restoration.[16] Comprehensive analyses demonstrated that the MenSC-hydrogel combination produced significantly smaller fibrotic areas, reduced pro-inflammatory cytokines, including TNF-α and IL-1β, increased anti-inflammatory factors such as IL-10 and TGF-β, and achieved markedly fewer IUAs with preserved glandular architecture.[16]

Building on these results, Pan *et al.* demonstrated enhanced efficacy when MenSCs were encapsulated within cross-linked hyaluronic acid scaffolds in mouse IUA models.[17] The biomaterial approach improved cell retention and local bioactivity compared to direct injection. Combination treatment resulted in superior regeneration outcomes, including increased endometrial thickness, restoration of functional glandular units, reduced cellular apoptosis and inflammation, and improved pregnancy rates, indicating genuine restoration of endometrial receptivity.[17]

MenSC therapy has also demonstrated efficacy in thin endometrium models (endometrial thickness less than 7mm).[10] Immunohistological analysis showed elevated expression of vimentin (stromal marker), cytokeratin 18 (CK18 – epithelial marker), and CD34 (endothelial marker), indicating robust angiogenesis.[18] Additionally, vascular endothelial growth factor (VEGF) expression was elevated, suggesting activation of pro-regenerative signalling pathways.[18]

Gene expression analysis revealed significant upregulation of implantation-related factors including leukaemia inhibitory factor (LIF), integrin-β3, and homeobox A10 (HOXA10), which are essential for establishing endometrial receptivity. Fertility testing demonstrated that MenSC-treated mice exhibited significantly increased pregnancy rates (52.38%) compared to untreated model mice (19.04%), demonstrating functional restoration of reproductive capacity.[18]

Mechanisms of therapeutic action

MenSC-mediated endometrial regeneration operates through multiple complementary mechanisms that work synergistically to restore tissue function. Paracrine signalling represents the primary mode of therapeutic action. MenSCs secrete a complex cocktail of bioactive molecules including growth factors (VEGF, EGF, IGF-1), cytokines, and extracellular vesicles that stimulate endogenous repair processes.[11,19] This secretome promotes proliferation of native endometrial cells and recruits host stem and progenitor cells to participate in tissue regeneration.[19]

Anti-fibrotic activity addresses one of the most challenging aspects of endometrial damage. Chronic injury often leads to pathological fibroblast-to-myofibroblast conversion and excessive scar formation. Research by Zhu *et al.* demonstrated that MenSCs directly inhibit fibrotic differentiation of endometrial stromal cells, blocking TGF-β-induced expression of myofibroblast markers like α-smooth muscle actin (α-SMA) and type I collagen.[8] Mechanistically, MenSCs activate the Hippo/TAZ pathway in stromal cells, effectively reversing the fibrotic phenotype.[8]

Angiogenesis and vascular repair constitute another mechanism. A healthy endometrium requires vascularisation, which is often compromised following injury. MenSCs promote vasculogenesis through secretion of pro-angiogenic factors, particularly VEGF. Treated tissues consistently show increased CD34+ endothelial cells and enhanced vascular density, ensuring adequate perfusion of regenerated endometrium.[8,16]

Immunomodulation creates a pro-regenerative tissue environment. Endometrial injury typically involves chronic inflammation that impedes healing.[20] MenSCs release anti-inflammatory cytokines and modulate immune cell populations, promoting regulatory T cell generation while inhibiting cytotoxic T cell activity.[12,13,21] This immunoregulatory function reduces chronic inflammation and establishes conditions favourable for tissue repair.[13,14,18]

Recent studies demonstrate that MenSCs can promote endometrial regeneration by modulating extracellular matrix remodelling. In a mouse model of IUA, MenSC treatment significantly reduced fibrosis through regulation of matrix metalloproteinase-9 (MMP-9) and plasminogen activator inhibitor-1 (PAI-1), restoring normal uterine architecture and improving pregnancy rates.[19]

Clinical translation: progress and challenges

Despite compelling preclinical evidence demonstrating consistent therapeutic efficacy across multiple animal models, clinical application of MenSCs for endometrial disorders remains in early developmental stages.

In a small prospective study (n=7) of women with severe Asherman's syndrome, Tan *et al.* reported that autologous menstrual blood-derived stromal cell transplantation increased endometrial thickness from ~3.9mm to ~7mm in five patients and resulted in two pregnancies after embryo transfer and one spontaneous pregnancy.[9] However, the authors emphasise that the method was uncontrolled and the sample size small, highlighting the need for larger scale randomised trials with standardised protocols.[9]

Several challenges must also be addressed for successful clinical translation. Cell characterisation and standardisation represent the most fundamental challenges. MenSCs currently lack universally accepted surface marker profiles, isolation protocols, or quality control standards that would enable consistent product development across laboratories and clinical centres. Populations isolated from menstrual blood may contain heterogeneous mixtures of endometrial stromal

fibroblasts, multipotent MSCs, epithelial cells, and other cell types in varying proportions. This variability complicates efforts to standardise cell products and establish meaningful potency assays for regulatory approval. Individual donor variation in cell characteristics may require personalised approaches or careful screening protocols.[22,23]

Manufacturing and scale-up challenges present practical obstacles. Autologous MenSC therapy requires sophisticated processes for sterile collection, efficient isolation, controlled expansion to therapeutic numbers, comprehensive quality control testing, and potentially cryopreservation – all under current good manufacturing practice conditions. No standardised production protocols exist that are specifically optimised for MenSCs, and the cost and complexity of establishing dedicated manufacturing facilities may limit accessibility.[22]

The ability of transplanted MenSCs to successfully engraft – that is, to survive, integrate, and persist in the uterine tissue – remains a critical unresolved question. Historical experience with endometrial stem cell applications have been hampered by low colonisation rates and uncertain long-term efficacy.[22] The duration of MenSC persistence in uterine tissue, extent of integration with host endometrium, and optimal timing and frequency of treatments remain undetermined. While biomaterial carriers can improve cell retention and outcomes, optimal delivery methods, dosing regimens, and treatment schedules for humans require systematic investigation.[22]

Safety assessment and long-term monitoring require increased investigation given the intended use in reproductive-age women. Although no serious adverse events have been reported and preclinical models demonstrate good biocompatibility, comprehensive long-term safety data are essential. Potential concerns requiring evaluation include risks of ectopic tissue formation, immune reactions, unregulated proliferation, and effects on future pregnancies. Optimal patient selection criteria, contraindications, and monitoring protocols need establishment through clinical experience.[7,22]

Menstrual blood preparations are inherently heterogeneous, with marker profiles and differentiation potential varying by donor cycle stage, collection day and isolation method.[24] Standardised protocols for isolating and expanding MenSCs are lacking,[25] leading to inconsistent cell potency and yield. Donor factors (age, hormonal status, contraceptive use) influence MenSC growth and phenotype, and sample sterility must be rigorously maintained.[26] Large-scale expansion is needed to reach therapeutic cell numbers, which is time consuming and can induce replicative senescence.[26] Autologous use is limited to premenopausal women; using banked or allogeneic MenSCs extends applicability but raises immune considerations despite MenSCs typically lacking human leukocyte antigen – DR isotype (HLA-DR – low immunogenicity).[26] This presents a major bottleneck for clinical applications that rely on donor-derived MenSCs. If transplanted into immunocompetent recipients without fully understanding their interaction with innate and adaptive immune cells, there is a risk of subclinical rejection or altered tissue response over time.[11] The immunomodulatory benefits of MenSCs are clear, but the long-term consequences of allo-reactivity remain uncertain. MenSC differentiation, while broad, is inconsistent: unpurified MenSCs often show reduced osteogenic/adipogenic capacity compared to bone marrow MSCs,[26] and passage-dependent drift can occur.[24] Engraftment of transplanted MenSCs appears low in animal models, suggesting that effects may be mainly paracrine.[25]

Regulatory challenges loom: good manufacturing practice-compliant culture and banking protocols, rigorous safety testing (tumourigenicity/genomic stability), standardised characterisation, and validated potency assays are needed before clinical use.[26]

To summarise, while MenSCs appear generally safe in preclinical studies, significant translational challenges remain. Long-term safety, optimal patient selection, and standardised monitoring protocols are not fully established, and potential risks, such as immune reactions, aberrant proliferation, and impacts on future fertility, require careful evaluation before widespread clinical application.

Future directions and conclusions

MenSCs possess compelling biological characteristics and practical advantages that make them highly attractive for endometrial regenerative medicine. Their non-invasive harvest, autologous nature, rapid proliferation, broad differentiation potential, and intrinsic relationship to endometrial tissue create a unique therapeutic platform. Preclinical studies consistently demonstrate their ability to repair damaged endometrium through multiple mechanisms, restoring both structure and function.[9,11,16]

However, clinical translation requires addressing key challenges in cell characterisation, manufacturing standardisation, and safety assessment.[22,23] Carefully designed clinical trials with standardised protocols, appropriate controls, and rigorous endpoints are essential to validate therapeutic efficacy and safety in human patients.

The field would benefit from establishing consensus definitions for MenSC phenotype, developing scalable manufacturing processes, and creating regulatory frameworks appropriate for this cell type. Additionally, investigation of combination approaches using biomaterial carriers or co-delivery with other therapeutic agents may enhance clinical outcomes.

Overcoming these challenges could make MenSC therapies a breakthrough for treating Asherman's syndrome, thin endometrium, and other endometrial disorders.

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The impact of short-form video consumption on attention span and student academic performance

Abstract

The rapid rise of short-form video platforms such as TikTok has transformed media consumption among young people. Their highly stimulating and algorithm-driven design raises concerns about excessive use, attention disruption, and potential negative effects on academic performance and mental well-being. The objectives of this article are to examine the relationship between addictive patterns of short-form video consumption and students' attention span, and to explore how reduced attention span influences academic performance and learning efficiency. Peer-reviewed studies, theoretical models, and empirical research were used to assess the cognitive, psychological, and academic impacts of short-form video consumption. The reviewed evidence suggests that addictive short-form video use is consistently associated with poorer mental health outcomes, reduced attention span, impaired academic performance, and disrupted sleep. The findings highlight that the academic risks associated with short-form video platforms are primarily driven by addictive rather than moderate use. Both theoretical and empirical evidence suggest that constant exposure to fast-paced, reward-driven content reshapes attentional habits, undermining students' capacity for deep learning and sustained concentration.

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Introduction

Short-form video has rapidly transformed the way people consume digital content. Platforms such as TikTok, Instagram Reels, YouTube Shorts, and Snapchat Spotlight now dominate online engagement, offering endless streams of bite-sized entertainment. Despite being relatively new, short videos have already surpassed mobile games as the most time-consuming and fastest-growing segment of the entertainment industry, with users spending an average of over 22 hours per month watching them.[1]

One reason for their addictive appeal lies in the rapid stimulation of the brain's reward system. Personalised recommendation algorithms deliver immediate gratification, with each swipe providing a dopamine hit that reinforces continued scrolling.[2] Over time, this cycle can contribute to patterns of overuse and, in some cases, social media addiction, particularly among younger audiences. TikTok, for example, has been shown to capture attention through tailored content and instant rewards, making it difficult for students to disengage.[3]

The COVID-19 pandemic (2020-2021) accelerated this surge, as lockdowns and social isolation led many students to spend more time online.[4] While these platforms offer entertainment and social connection, they also encourage excessive and passive consumption, often described as 'doomscrolling'. This phenomenon has raised growing concerns about its impact on students' attention, study habits, and academic outcomes.[5] This article examines the relationship between short-form video consumption and academic performance, highlighting both the risks and the implications for student life.

TikTok's effect on media and media consumption

TikTok is one of the most widely used social media platforms among young people, with 35% of users aged between 16 and 24 years.[6] The platform reports approximately 1.5 billion monthly active users, reflecting the global penetration of this application.[7] It is reported that 90% of users visit it on a daily basis, with an average daily usage of 52 minutes.[8,9]

In response to growing usage concerns, Chao *et al.* examined the association between TikTok use and mental health by comparing students with varying levels of social media engagement.[10] The study included 1,346 students from three schools in China, with an average age of approximately 15 years. Participants were categorised as non-users, moderate users, and addicted users based on their engagement with short video platforms. Adolescents classified as addicted users demonstrated significantly poorer mental health outcomes, including higher levels of depression, anxiety, stress, and loneliness, as well as social difficulties such as social anxiety, attention problems, and reduced life satisfaction.[10] In contrast, moderate users did not differ from non-users in terms of mental health outcomes.

Addicted users experienced greater stress and weaker academic performance, along with higher levels of bullying and victimisation, whereas no significant differences in academic performance or mental health were observed between moderate and non-users. Family environment also differed across groups: non-users demonstrated the most advantageous family conditions, including better parental relationships, while addicted users were more likely to experience negative parenting styles and come from families with lower parental education levels.[10] Although moderate users showed some differences in family environment compared to non-users, these differences did not translate into poorer mental health or academic outcomes. Additionally, poor sleep quality was significantly associated with addictive TikTok use, whereas no such associations were observed among moderate or non-users.[10]

Despite being relatively new, short videos have already surpassed mobile games as the most time-consuming and fastest-growing segment of the entertainment industry, with users spending an average of over 22 hours per month watching them.

In summary, this study demonstrates that academic difficulties are most evident among students who engage in addictive, rather than moderate, short-form video use.[10] Attentional difficulties, poor sleep quality, and elevated stress among addicted TikTok users suggest mechanisms through which excessive short-form video consumption may reduce sustained concentration and learning efficiency.

How attention span is defined and understood in educational settings

Attention span refers to the duration of time an individual can maintain focused mental effort on a particular task before becoming distracted.[11] According to Haliti-Sylaj and Sadiku, attention span is a key determinant of learning effectiveness, as sustained attention allows students to process, understand, and store new information. In educational contexts, it supports engagement, comprehension, and long-term memory formation.[12] The traditional view that students' attention declines irreversibly after 10-15 minutes of lecture has been

questioned in recent years. As argued by Bradbury, this commonly cited "15-minute limit" lacks empirical evidence and is largely based on misinterpreted studies of note taking rather than true cognitive attention.[13] Bradbury's review concludes that attention span is not a fixed biological limit but a dynamic, situational construct influenced by factors such as the lecturer's delivery style, the student's motivation, and the relevance of the material.[13] Therefore, attention in educational settings should be understood not as a strict time constraint, but as a flexible process that can be enhanced through engaging teaching methods and learner motivation.[13]

Both behavioural and neuroscientific evidence support the idea that longer attention spans enable students to maintain concentration and achieve deeper comprehension during learning activities.

Zeqiri found that undergraduate students with extended attention spans, particularly those able to focus for 45 minutes or more, have reported higher engagement, better understanding of lecture content, and fewer concentration lapses compared to peers who lost focus after 20-30 minutes.[14] Students with sustained attention described being more capable of processing information continuously, leading to improved retention of material.[14] Complementing these behavioural findings, a scoping review by Zeng *et al.* synthesised 16 neuroimaging studies and demonstrated that sustained classroom attention is associated with specific neural markers, including increased brain-to-brain synchrony between students and teachers, and decreased alpha-band power, both of which predicted higher comprehension and better memory performance.[15] Together, these findings indicate that prolonged intentional engagement not only facilitates focus during lectures, readings, and assignments, but also supports the neural mechanisms essential for effective information encoding and long-term knowledge retention.

Both behavioural and neuroscientific evidence support the idea that longer attention spans enable students to maintain concentration and achieve deeper comprehension during learning activities.

Short-form video consumption and the decline of attention span

Frequent exposure to short-form video content, such as TikTok and Instagram Reels, has been shown to shorten attention span by conditioning the brain towards rapid attentional shifts and superficial processing. In their 2015 paper, Loh and Kanai argue that the internet and social media environments promote "shallow information processing", in which users constantly switch focus between stimuli rather than engaging in sustained cognitive effort.[16] This habitual multitasking reinforces impulsive, reward-driven attention patterns and weakens executive control mechanisms within the prefrontal cortex, impairing the ability to maintain prolonged focus.[16]

Similarly, a 2019 paper by Lodge and Harrison found that digital multitasking and the fragmented presentation of online information reduce working memory capacity, comprehension, and information retention during learning.[17] They note that modern digital platforms exploit involuntary attention systems through constant novelty and sensory stimulation, making it increasingly difficult for individuals to maintain deep, sustained attention.[17] Together, these findings suggest that habitual consumption of short, rapidly changing video content contributes to cognitive adaptation that favours immediate gratification at the expense of sustained concentration and long-term learning efficiency.

Frequent exposure to short-form video content, such as TikTok and Instagram Reels, has been shown to shorten attention span by conditioning the brain towards rapid attentional shifts and superficial processing.

Short-form video platforms such as TikTok continually overload and fragment the brain's attentional system through rapid content transitions and reward-driven feedback loops.[18] Each brief clip delivers a novel stimulus that activates the brain's dopaminergic reward circuitry, reinforcing compulsive scrolling and conditioning users to seek immediate stimulation rather than sustained focus. From the perspective of cognitive load theory (1998), which suggests that the brain has a limited capacity for processing information at a given time, this constant barrage of stimuli consumes the brain's limited working memory capacity. This leads to cognitive fatigue and diminishing the ability to process or retain academic material.[19,20] Similarly, Kahneman's 1973 theory of attentional resources suggests that attention operates as a finite pool that becomes depleted through continuous engagement with fast-paced, high-intensity content, leaving fewer resources available for slower, effortful tasks such as reading or studying.[21] The selective attention model proposed by Treisman as far back as 1964 explains how the emotionally charged and personalised nature of short videos penetrates

attentional filters, drawing focus away from learning-related material.[22] Behaviourally, this aligns with findings from Loh and Kanai[16] and Lodge and Harrison,[17] who demonstrated that rapid digital multitasking and reward-based engagement promote shallow processing and weaken sustained attention over time. Together, these theories suggest potential mechanisms through which short-form media may systematically reshape cognitive habits, training the brain towards fragmented attention, and reducing its capacity for deep comprehension and long-term knowledge retention.

Attention span and its impact on academic performance and concentration challenges

A growing body of research demonstrates that shortened attention spans, often resulting from constant digital stimulation, significantly impair students' academic outcomes. Fillmore (2015) found that daily internet use fosters shorter attention spans among young adults, reducing their ability to sustain concentration on complex academic tasks.[23] Similarly, Asif *et al.* conducted a mixed-methods study showing that excessive short-form video consumption correlates with lower exam performance and self-reported focus difficulties.[24] Students frequently described symptoms such as distraction, procrastination, and difficulty engaging with lengthy reading materials, behaviours consistent with dopamine-driven reward cycles that condition the brain for rapid novelty rather than sustained cognitive effort.[24] Together, these studies provide empirical evidence that diminished attention span limits students' capacity to process information deeply, maintain focus across extended periods, and achieve optimal academic performance.

Beyond academic outcomes, reduced attention span contributes to broader cognitive difficulties, including mind wandering, task-switching inefficiency, and weakened working memory. Hayat *et al.* demonstrated that constant digital multitasking imposes a heavy cognitive load, fragmenting attention and overtaxing working memory over time. Their findings indicate that habitual task switching fosters disjointed focus and mental fatigue, diminishing the brain's ability to sustain goal-directed attention.[25,26] Similarly, Ellah *et al.* observed that students with shorter attention spans performed poorly on problem solving tasks, as frequent attentional lapses disrupted information encoding and memory retention.[27] This underscores that reduced attention span undermines executive functioning by lowering cognitive control, increasing distractibility, and impairing the capacity for sustained, high-level thought.

However, attention span alone does not fully account for academic underperformance. Emerging evidence highlights the role of mediating lifestyle factors such as sleep quality, diet, and physical activity in shaping both attention and learning outcomes. Burns *et al.* found that adolescents who maintained adequate sleep, regular exercise, and balanced nutrition had significantly higher academic achievements compared to peers who did not.[28] Likewise, Yadav reported that medical students with poor sleep and irregular eating habits experienced greater cognitive fatigue, reduced attention, and lower learning efficiency.[29] These findings suggest that attention span operates as both a mediator and a consequence of broader health behaviours: poor lifestyle patterns erode attentional control, which in turn diminishes academic performance. Consequently, interventions that promote sleep hygiene, balanced diet, and regular physical activity may indirectly enhance attention and support long-term academic success. Decreasing quality of mediating lifestyle factors is both a documented symptom of and can be exacerbated by short-form video overconsumption.[30] These interventions/lifestyle changes can help to improve attention span by supporting the individual in tackling the root addiction.[31]

Emerging evidence highlights the role of mediating lifestyle factors such as sleep quality, diet, and physical activity in shaping both attention and learning outcomes.

Solutions to improve attention span

Recent studies propose multiple behavioural and technological strategies to enhance attention span and mitigate the cognitive effects of short-form video overuse. Haliti-Sylaj and Sadiku suggest

incorporating mindfulness training, digital detox routines, and time management techniques to strengthen sustained focus and reduce impulsive media engagement.[12] Asif and Kazi emphasise digital well-being applications (such as Screen Time or Forest) and media literacy programmes that educate students about the dopamine-driven reinforcement loops underlying short video algorithms.[24] Hayat *et al*. advocate cognitive load regulation methods such as single tasking and structured study intervals (such as the Pomodoro technique), while also highlighting the potential of artificial intelligence (AI)-assisted focus tools and brain–computer interfaces to monitor and support concentration in real time.[26] Complementing these approaches, Subramanian stresses that attention can be enhanced when learning materials are personally meaningful and interactively engaging, suggesting that educational design itself can act as an attention-building intervention.[32]

Evidence from systematic reviews suggests that digital detox interventions are associated with short-term improvements in attention and cognitive functioning.[33] Experimental studies report enhanced focus and reduced cognitive overload following reduced digital engagement.[33] However, this evidence is largely based on general digital user populations rather than students with high levels of short-form video consumption, limiting direct generalisation to this group.[33]

In addition to digital detox approaches, mindfulness-based interventions have been shown to produce measurable improvements in sustained attention and attentional control. Reviews of clinical and adolescent populations report gains in task focus, conflict monitoring, and executive attention following mindfulness training. While these findings suggest potential benefits for attentional regulation, most evidence derives from persons with ADHD or clinical samples, rather than students affected by short-form video overuse.[34]

Beyond individual cognitive strategies, interventions aimed at regulating digital interruptions and screen-based distractions have demonstrated practical benefits for student attention.[35] Studies involving university students indicate that training focused on managing interruptions and study behaviour can lead to significant improvements in self-reported attention and reduced digital distraction.[35] Nevertheless, small sample sizes and reliance on subjective measures limit the generalisability of these findings.[35]

Limitations of current interventions and gaps for future research

Despite promising results, current interventions to improve attention span face notable limitations. Many existing studies rely on self-reported measures, short intervention durations, and small, homogenous samples, which reduce generalisability.[12,36] Moreover, few have objectively tracked neurocognitive changes over time, leaving uncertainty about whether attention improvements are temporary or sustained.[16] Most interventions also fail to account for individual variability in attention regulation, such as differences in baseline cognitive capacity, sleep, or mental health. Subramanian further critiques that current models often treat attention as a fixed resource rather than a skill adaptable to context.[32] Therefore, future research should employ longitudinal, multi-method designs that integrate electroencephalogram (EEG) or eye-tracking measures, include cross-cultural and age-diverse samples, and evaluate how lifestyle factors interact with digital media exposure. Such studies would clarify the mechanisms through which attention can be trained and sustained, ultimately guiding more evidence-based educational and clinical interventions.

Despite promising results, current interventions to improve attention span face notable limitations.

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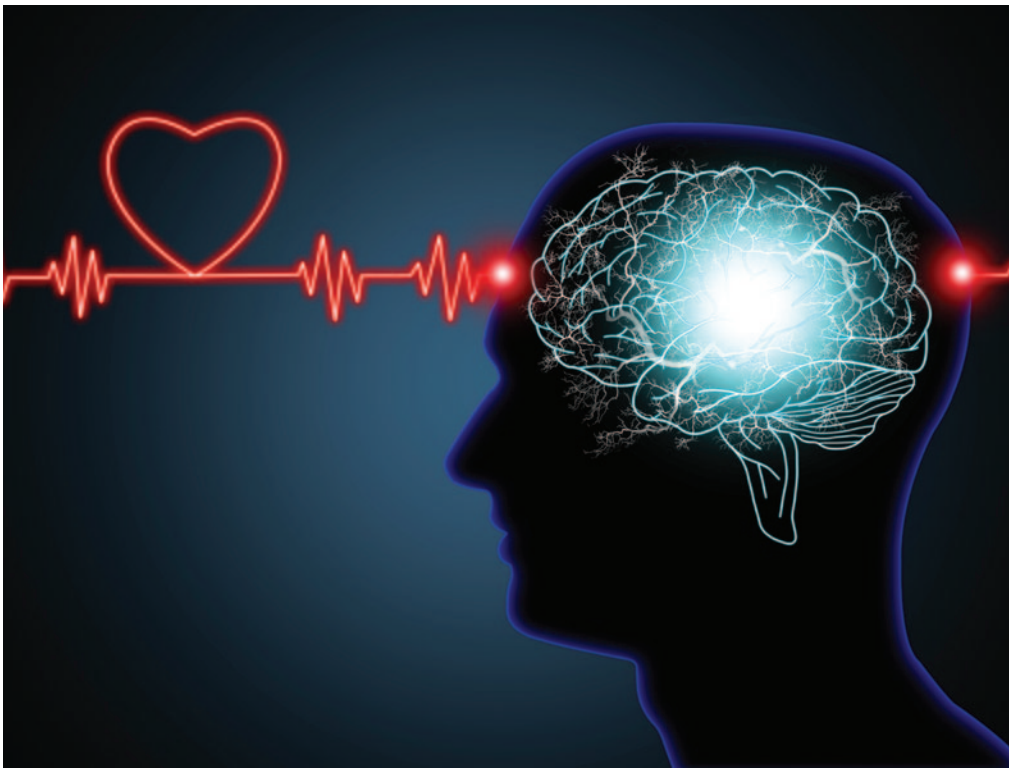
The relationship between Takotsubo cardiomyopathy and neurological disease



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Declaration of generative AI
During the preparation of this manuscript, the author(s) used generative artificial intelligence (GenAI) to assist, where applicable, with language editing, sentence refinement, and improvement of readability. All content generated or modified using these tools was carefully reviewed and verified by the author, who takes full responsibility for the integrity, accuracy, and originality of the work.

Abstract

Takotsubo cardiomyopathy (TCM), also known as stress-induced cardiomyopathy or "broken heart syndrome", is a transient form of left ventricular dysfunction that often mimics acute coronary syndrome. While the exact pathophysiology remains undetermined, mounting evidence highlights the importance of the neurocardiac axis in precipitating this condition. Neurological disorders such as subarachnoid haemorrhage, traumatic brain injury, seizures, and autoimmune encephalitis have been increasingly associated with TCM, highlighting the role of sympathetic hyperactivation and catecholamine surges in myocardial stunning. This review synthesises current knowledge of TCM's pathophysiological mechanisms, with emphasis on the interplay between neuroendocrine stress, receptor-level signalling, microvascular impairment, and hormonal vulnerability. Further examination of clinical associations between neurological insults and TCM outlines their implications for diagnosis and management in neurocritical care. Finally, future directions are discussed, including the need for prospective studies, mechanistic research, and interdisciplinary frameworks that integrate neurology and cardiology. A deeper understanding of this neurocardiac interface could improve patient outcomes and refine therapeutic strategies.

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Introduction

Takotsubo cardiomyopathy (TCM), also known as stress-induced cardiomyopathy or "broken heart syndrome", is a transient cardiac condition characterised by acute left ventricular dysfunction.[1] It is typically triggered by intense emotional or physical stress, often mimicking acute coronary syndrome.[1] However, TCM patients usually present with normal coronary arteries on angiography, distinguishing it as a unique and reversible form of cardiomyopathy.[1]

The hallmark imaging finding of TCM is the apical ballooning of the left ventricle, which resembles the shape of a Japanese "takotsubo" octopus trap. However, over time, variants such as mid-ventricular, basal, and focal patterns have also been classified.[2] Clinical presentations often include chest pain, ST-segment elevation or T-wave inversion on an electrocardiogram (ECG), modest troponin elevations, and left ventricular wall motion abnormalities.[3]

While the exact pathophysiology remains unconfirmed, a growing body of evidence points towards a significant neurocardiac axis. It is believed that a surge in catecholamines, such as norepinephrine and epinephrine, in response to stress from either peripheral sympathetic activation or direct central nervous system activation, plays a central role in myocardial stunning. Excessive catecholamines may cause structural alterations, including contraction band necrosis, mild neutrophil infiltration, and increased extracellular matrix.[4] Oxidative stress and disrupted calcium handling have also been implicated in the contractile dysfunction seen in TCM.[5] Interestingly, the PI3K-AKT pathway, a cell survival cascade, appears to protect cardiomyocytes from cell death and aid in their rapid regeneration.[6] Furthermore, studies suggest that central nervous system lesions or dysfunction, including stroke, epilepsy, subarachnoid haemorrhage and neuroinflammatory conditions, may precipitate TCM through autonomic dysregulation.[7]

Recent data from the international German-Italian-Spanish Takotsubo (GEIST) registry indicate that roughly one in six TCM patients (17%) had an underlying neurological disorder, most commonly prior cerebrovascular events, neurodegenerative disease, migraine, epilepsy, or brain tumours.[8] Compared with patients without neurological comorbidities, these individuals experienced significantly longer hospital stays (median eight vs six days), a higher rate of in-hospital complications (27% vs 16%), and increased mortality. Mortality at 60 days was almost three times higher (8.8% vs 3.4%), while long-term mortality more than doubled (23.5% vs 10.1%).[8] Among the different phenotypes, patients with neurodegenerative disorders demonstrated the poorest prognosis, with long-term mortality approaching 30%, while patients with migraines were generally associated with better outcomes.[8]

This article will explore the relationship between neurology and cardiology in the context of TCM, shedding light on rare but clinically relevant cross-linkages between the two domains, and outlining how disruptions in the central nervous system can influence cardiac function, with implications for clinical diagnosis and management.

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Pathophysiology and mechanisms

TCM results from interplay between neuroendocrine surges, regional myocardial receptor signalling, microvascular impairment, and hormonal vulnerability. The catecholamine storm, comprised of elevated epinephrine and norepinephrine, remains the trigger. These agents are directly toxic to the myocardium, and prompt acute myocardial stunning that mirrors stress-triggered cardiomyopathies in experimental models.[9] Moreover, the condition is further exacerbated by microvascular dysfunction, where impaired coronary microcirculation manifests as endothelial dysfunction, vasospasm, and delayed perfusion in the ballooned myocardial segments, compounding contractile impairment.[10]

Notably, the predominance of TCM in postmenopausal women implicates oestrogen deficiency as a potential predisposing factor.[11] Oestrogen loss impairs endothelial function and diminishes cardiovascular resilience against stressors, and may exaggerate catecholaminergic effects in vulnerable myocardial regions.[11]

Stress-induced activation between the neocortex, limbic system, brainstem, and spinal cord initiates sympathetic activation and adrenergic excess. The locus coeruleus, the major site of noradrenaline synthesis, is stimulated by emotional or physical stress. It receives afferent signals from the amygdala, hypothalamus, and cingulate gyrus.[12] This activation triggers the hypothalamic-pituitary-adrenal axis and the adrenal medulla, resulting in an increase in plasma catecholamine, often two to three times normal serum levels. This elevation in catecholamines amplifies cardiac sympathetic innervation and myocardial vulnerability.[13] Thus, emotional and neurological triggers may directly translate into transient ventricular dysfunction, highlighting the central role of neurocardiac coupling in this condition.[14]

At the molecular level, catecholamine exposure induces a beta-2 adrenergic receptor (beta2-AR) signalling switch from G(s) to G(i) coupling. This is known as "stimulus-directed trafficking".[15]

Switching significantly diminishes myocardial contractility, especially in the left ventricular apex where beta2-AR density is greatest, producing the hallmark apical ballooning of TCM. This was demonstrated in an experimental model where high-dose epinephrine triggered apical hypokinesis via beta2-AR-G(i) signalling. Blocking this pathway prevented the effect, confirming its role in TCM pathophysiology.[16]

Complementing this, histological data from TCM patients demonstrate increased myocardial expression of G protein-coupled kinase 2 (GRK2) and beta-arrestin 2, proteins central to beta-AR desensitisation and G protein switching.[17] Beta-AR desensitisation refers to the phosphorylation-dependent uncoupling of beta-adrenergic receptors from stimulatory signalling, a protective mechanism to limit excessive catecholamine-driven myocardial injury. Their membrane expression during the acute phase provides the first human biopsy-based evidence of such adaptive signalling.[17] Simultaneously, metabolic stress driven by oxidative damage, mitochondrial dysfunction, and calcium overload worsens myocardial function. Catecholamines can exacerbate this by activating beta-ARs coupled to the stimulatory G(s) protein, triggering the adenylyl cyclase-cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) pathway. This cascade promotes excessive calcium influx, reactive oxygen species generation and mitochondrial injury, amplifying cardiomyocyte dysfunction. As a result, these molecular derangements collectively contribute to the reversible, yet profound, myocardial stunning seen in TCM.[15]

TCM arises from the convergence of sudden neurogenic stimulus, receptor-level adaptations, microvascular fragility, metabolic imbalance, and hormonal susceptibility. Together, these mechanisms explain the unique and reversible myocardial stunning pattern seen in TCM. Understanding this convergence lays the groundwork for exploring how neurological disorders with their own autonomic and neuroendocrine signatures modulate TCM presentation and outcomes.

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TCM-associated neurological disease

TCM is increasingly recognised as a significant complication of various acute neurological insults. This highlights the neurocardiac axis, where neurological injury can precipitate transient myocardial dysfunction through sympathetic hyperactivation, catecholamine surges, and autonomic dysregulation.

TCM has been reported in up to 9% of patients with aneurysmal subarachnoid haemorrhage (aSAH).[18] In a 2025 cohort study, roughly one-third of aSAH patients who subsequently developed TCM achieved favourable neurological outcomes despite the dual burden of cerebral and myocardial injury.[18] The pathophysiology is thought to involve a catecholamine-driven myocardial stunning, compounded by impaired cerebral perfusion pressure. These findings underscore the importance of early cardiac screening and multidisciplinary management in aSAH complicated by TCM.

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Characterised by basal hypokinesia and apical hyperkinesia, the onset of reverse TCM (rTCM) was described in a unique case report following a stereotactic brain biopsy.[19] Like classic TCM, rTCM is commonly associated with neurological triggers, most notably intracranial haemorrhage, suggesting that neurosurgical procedures can precipitate TCM. Given the potential for haemodynamic instability and atypical presentations, careful perioperative investigation and cardiac vigilance are essential in high-risk neurosurgical settings, including early ECG monitoring, serial cardiac biomarker assessment, and low-threshold echocardiography to detect evolving ventricular dysfunction or arrhythmias.

TCM has also been reported in patients with Bickerstaff brainstem encephalitis (BBE), a rare post-infectious autoimmune encephalitis caused by autoantibodies against gangliosides.[20] Emphasising the role of neuroinflammation as a trigger within the neurocardiac axis, a documented case following COVID-19 showed that TCM developed alongside BBE but resolved after immunotherapy, suggesting that brainstem inflammation and autonomic dysregulation may directly precipitate cardiomyopathy.[21]

Although less common, TCM has been reported following traumatic brain injury (TBI), typically occurring within the first few days after the insult. One case described a 30-year-old male who developed TCM three days post severe TBI in the context of an associated subdural

haemorrhage, presenting with hypotension and elevated cardiac enzymes.[22] Echocardiography revealed apical hypokinesis with basal hyperkinesis and a significantly reduced ejection fraction, which normalised by day 20.[22] The proposed mechanisms include acute sympathetic activation and neurogenic catecholamine release, particularly in the setting of concomitant intracranial haemorrhage, rather than isolated TBI alone. Importantly, population-level data suggest that TCM is more strongly associated with haemorrhagic and epileptic neurological insults than with TBI itself.[23] These findings highlight the importance of maintaining suspicion of cardiac dysfunction in patients with severe TBI, especially when complicated by intracranial bleeding or unexplained haemodynamic instability.

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Additional reports describe TCM in settings such as acute intracranial haemorrhage, brain death states, and post-epileptic (Todd's) paresis.[24] In a recent systematic review of epilepsy-associated TCM cases, recurrent temporal associations between seizure activity and acute left ventricular dysfunction were identified, with most patients demonstrating reversible systolic impairment and favourable cardiac recovery.[24] Similarly, cases linked to Todd's paresis support the role of post-ictal sympathetic hyperactivity in triggering myocardial stunning.[25] For instance, a patient with focal post-ictal paresis immediately followed by ECG changes and echocardiographic evidence of TCM illustrated a temporal relationship between seizure-related autonomic surges and myocardial dysfunction.[25] Collectively, these associations reinforce the concept that diverse neurological insults, whether structural, inflammatory, or metabolic, can precipitate both classic and variant forms of TCM.

Together, these observations demonstrate that neurological insults can act as powerful triggers for TCM.

Clinical implications and management

The recognition of TCM in neurological settings carries important clinical implications, particularly in intensive care environments where neurocritical patients are at heightened risk. Given the strong association between acute neurological insults and TCM, routine cardiac evaluation should be considered in patients presenting with seizures, intracranial haemorrhage, TBI, or unexplained haemodynamic instability.[26] Initial workups should include serial ECGs, cardiac enzyme measurements, and transthoracic echocardiography to differentiate TCM from acute coronary syndromes and other cardiac emergencies.[26,27] Early identification enables appropriate supportive care and prevents mismanagement, such as unnecessary thrombolysis in cases misdiagnosed as myocardial infarction.[28]

Long-term care requires close outpatient follow-up to monitor recovery of left ventricular function, which typically normalises within weeks to months. However, recurrence occurs in up to 8% of cases and is more common in patients with chronic neurological or psychiatric conditions.[2] In high-risk populations, education on stress mitigation,[29] optimisation of antiepileptic adherence,[30] and regular cardiac assessments[31] may help to reduce the risk of recurrence. Hence, early detection and integrated management strategies can significantly improve both neurological and cardiovascular outcomes.

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Future directions and research gaps

Despite growing awareness of TCM's link to neurological disorders, significant knowledge gaps remain. Most evidence arises from case reports and small observational studies, limiting the ability to establish aetiology or quantify risk. Prospectively, multicentre studies are urgently needed to define incidence, prognosis, and recurrence rates among neurological subgroups, particularly in patients with subarachnoid haemorrhage, seizures, and autoimmune encephalitis.[32] Future research should explore the mechanistic underpinnings of the neurocardiac axis, where advanced neuroimaging techniques, such as functional magnetic resonance imaging and positron emission tomography, could help to map limbic-autonomic pathways involved in TCM onset. Additionally, circulating biomarkers of sympathetic activity (plasma catecholamines), inflammation (C-reactive protein [CRP] or interleukin 6 [IL-6]), and myocardial injury (b-type natriuretic peptide or troponins) may aid in risk stratification.[12] Furthermore, integration of continuous cardiac monitoring in neurocritical settings, such as serial troponin measurements, bedside echocardiography, or ECG telemetry could improve early detection of TCM-related fluctuations. These changes include identifying evolving patterns of ST-segments, arrhythmias, or

left ventricular wall abnormalities. Interventions such as optimised haemodynamic support and targeted cardioprotective strategies could mitigate irreversible myocardial damage.

Interdisciplinary research frameworks spanning neurology, cardiology, and critical care are needed. This would include an effective improvement in TCM phenotypes across neurological disorders, generating risk-stratified, tailored management algorithms, testing whether emerging therapies, such as targeted beta-adrenergic modulation, neuroprotective interventions, or other novel strategies could reduce events in high-risk patients.[33]

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Some examples of ongoing neurocardiac studies providing further insight include the PRediction of Acute coronary syndrome in acute Ischemic StrokE (PRAISE) study, where the aim is to evaluate whether dynamic troponin patterns in acute stroke identify occult coronary disease, informing interpretation of neurogenic troponin rises.[34] Cardiac magnetic resonance imaging-led protocols such as CORONA-IS aim to distinguish neurogenic myocardial stunning from chronic ischaemia, while BROKEN-SWEDEHEART is testing adenosine, dipyridamole, and apixaban to hasten recovery and prevent thrombosis in TCM.[35,36] Advancing mechanistic understanding and evidence-based care through prospective multicentre studies, advanced imaging, and biomarker-driven strategies should improve outcomes and clarify the neurocardiac interface.

Conclusion

TCM lies at the intersection of cardiology and neurology, reflecting the complex interplay between sympathetic surges, receptor-level adaptations, microvascular dysfunction, and hormonal factors. Its association with diverse neurological insults emphasises the need for vigilance in neurocritical care. Although current treatment remains largely supportive, emerging research highlights opportunities for targeted interventions and novel frameworks that unite neurological and cardiovascular expertise. By strengthening these collaborations and addressing existing research gaps, we can move towards more precise risk stratification, earlier detection, and improved long-term care for patients with TCM.

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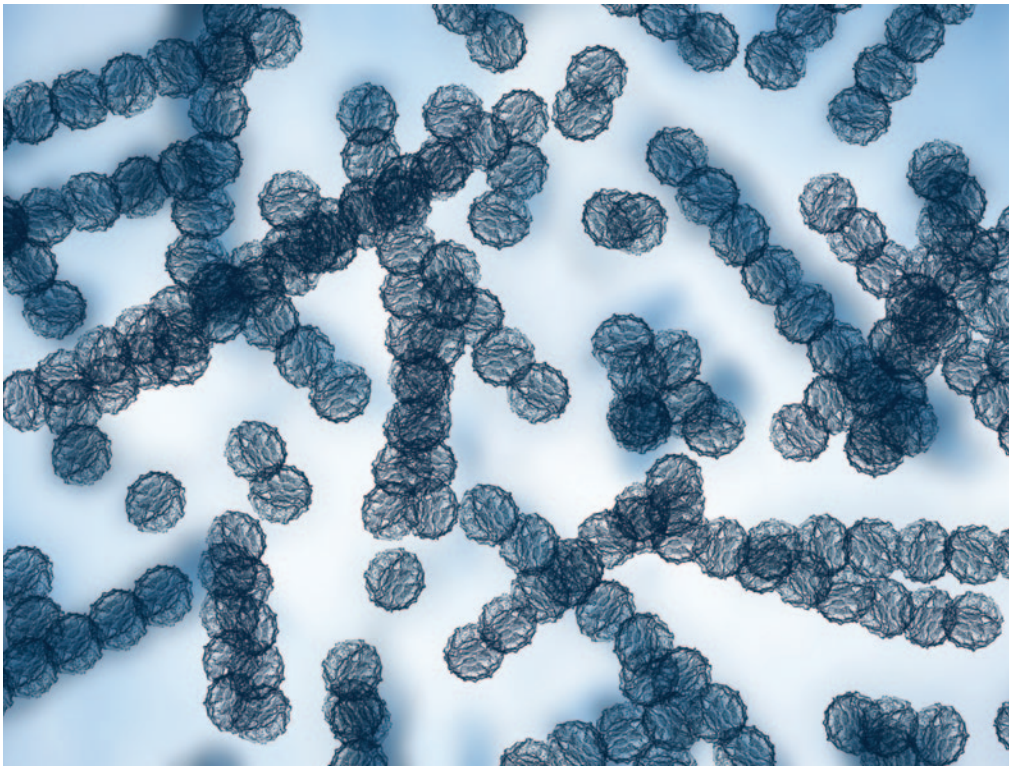
The rising global burden of invasive fungal infections: emerging threats and innovative therapeutics



Abstract

Invasive fungal infections represent a growing and often overlooked threat to global health, with substantial mortality and morbidity worldwide. Increasing populations with impaired immunity, the rise of resistant organisms such as *Candidozyma auris*, and changes in environmental conditions have contributed to the expansion of fungal disease into new regions. Recent outbreaks, including those associated with COVID-19, demonstrate the complex interaction between patient vulnerability, healthcare delivery, and pathogen traits. Treatment options remain constrained by limited drug classes and emerging resistance, but novel antifungal agents with unique targets, improved pharmacokinetics, and broader activity are expanding therapeutic possibilities. Advances in rapid diagnostics and individualised treatment strategies enable earlier intervention and optimised outcomes. Co-ordinated efforts in access to therapy, surveillance, and antifungal stewardship are essential to reduce disease burden. Comprehensive strategies integrating these approaches are critical to mitigating the impact of invasive fungal infections globally.

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Introduction

Fungal pathogens constitute a major and growing threat to global health, yet they have long remained neglected in comparison with bacterial and viral agents. Invasive fungal diseases are estimated to cause several million life-threatening infections and more than 2.5 million deaths annually worldwide, a burden comparable to that of tuberculosis or malaria, but with substantially lower investment in surveillance, diagnostics, and drug development.[1,2] This disparity has contributed to limited awareness of and delayed responses to emerging fungal threats.

Multiple converging factors have driven the recent rise in severe fungal infections. The number of individuals with impaired immunity has increased steadily due to advances in solid organ and haematopoietic stem cell transplantation, intensive cancer chemotherapy, and widespread use of biologic and targeted immunomodulatory therapies.[3] These populations are highly vulnerable to opportunistic fungi such as *Aspergillus* species, *Mucorales*, and non-albicans *Candida*. In parallel, the emergence and global spread of *Candidozyma auris* (*C. auris*, formerly *Candida auris*) have underscored the capacity of fungi to cause sustained healthcare-associated outbreaks, display resistance to multiple antifungal classes, and evade routine laboratory identification.[4] In recognition of this escalating threat, the World Health Organization (WHO) has published its first fungal priority pathogen list, highlighting the urgent need for improved prevention, diagnosis, and treatment of high-priority fungal pathogens.[1]

Environmental change may further amplify this risk. Rising global temperatures have been proposed to facilitate adaptation of environmental fungi to mammalian thermal tolerance, potentially expanding the pool of species capable of causing human disease.[5] Despite these developments, the antifungal armamentarium has remained limited to a small number of drug classes until very recently, with resistance increasingly reported.[3,6] Mortality from invasive fungal infections frequently exceeds 40%, compounded by diagnostic delays and limited access to sensitive mycological testing.[4] Together, these factors highlight fungal infections as an escalating and underappreciated public health challenge. This review examines emerging fungal threats, recent advances in antifungal therapeutics, and future directions required to address the growing global burden of fungal disease.

Emerging fungal threats: resistance and spread

Among emerging fungal threats, *C. auris* stands as one of the most concerning pathogens identified in the 21st century. First described in 2009, this yeast has rapidly disseminated globally and is now recognised as a WHO critical priority fungal pathogen due to its propensity for healthcare-associated transmission, environmental persistence, and resistance to multiple antifungal classes.[7] Meta-analyses of clinical isolates from 2015 through early 2024 indicate extraordinarily high pooled prevalence of resistance to fluconazole (~92.5%), voriconazole (~49%), and amphotericin B (~51%) among *C. auris* strains, underscoring the multidrug-resistant phenotype that complicates therapy.[8] Studies from tertiary care centres show that *C. auris* accounts for a growing proportion of nosocomial candidaemia, often surpassing traditional *Candida* species and correlating with invasive device use, steroid exposure, and abdominal surgery.[9] Outbreak investigations in diverse geographies demonstrate that *C. auris* spreads readily within healthcare settings, and is frequently linked to mechanical ventilation, shared care environments, and lapses in infection control, leading to persistent endemicity in some institutions.[9]

Beyond *C. auris*, the geographic distribution of other fungal pathogens is shifting in response to climate change, with documented expansion of ecological niches and increased incidence of endemic mycoses such as coccidioidomycosis, histoplasmosis, and blastomycosis into regions previously considered non-endemic.[10] These changes are attributable to rising global temperatures, altered precipitation patterns, and soil disturbance, which can enhance spore aerosolisation and broaden spore-bearing habitats, thereby exposing new human populations to infection.[10] Surveillance data from the United States illustrate this trend, with over 21,000 cases of these endemic mycoses reported annually and geographic spread consistent with climatic and environmental shifts.[10] Similarly, public health reports in 2024 document record highs for coccidioidomycosis in California and expansion into northern territories, likely driven by drought and rainfall variability linked to climate change.[5] These infections outside historic endemic ranges highlight a climate-mediated risk that demands enhanced awareness and surveillance.

The COVID-19 pandemic further exemplifies how host factors and healthcare pressures potentiate opportunistic fungal outbreaks. COVID-19-associated mucormycosis (CAM) and aspergillosis surged in India and neighbouring regions during 2020-2021, with some estimates suggesting thousands of cases occurring in association with or shortly after SARS-CoV-2 infection.[11] A systematic review encompassing nearly 1,000 cases demonstrated that corticosteroid use and uncontrolled diabetes were highly prevalent among CAM patients, and overall mortality approached approximately 39%.[11] This outbreak revealed the interaction between iatrogenic immunosuppression, metabolic derangements, and fungal invasion, and highlighted the vulnerability of heavily affected health systems during pandemic surges.

Table 1: Summary of emerging antifungal therapies.[19]

Indication	Current options	Emerging options	Rationale
Antifungal prophylaxis	Triazoles, inhaled amphotericin B	Rezafungin, ibrexafungerp, opelconazole	Long-acting IV, oral, and inhaled agents may improve adherence and tolerability
Candidiasis	Echinocandins, fluconazole	Rezafungin, fosmanogepix, ibrexafungerp	Active against azole- and echinocandin-resistant *Candida*; oral option with ibrexafungerp
Aspergillosis	Triazoles, echinocandins	Fosmanogepix, olorofim, opelconazole	Options for azole-resistant disease; oral (fosmanogepix, olorofim) and inhaled (opelconazole) approaches
Pneumocystosis	Trimethoprim–sulfamethoxazole, atovaquone	Rezafungin	Likely role in prophylaxis or adjunctive therapy rather than treatment
Cryptococcosis	Amphotericin B, fluconazole, flucytosine	Encochleated amphotericin B	Emphasis on reduced toxicity and simplified induction therapy
Mucormycosis	Amphotericin B, triazoles	Encochleated amphotericin B	Focus on safer amphotericin delivery and outpatient feasibility
Endemic mycoses	Amphotericin B, itraconazole	Encochleated amphotericin B, olorofim (coccidioidomycosis)	Potential oral or less toxic alternatives for severe or refractory disease
Scedosporiosis/ lomentosporiosis/fusariosis	Amphotericin B, triazoles, terbinafine	Fosmanogepix, olorofim	High unmet need; primarily salvage or combination therapy settings

Advances in antifungal therapy

Current antifungal therapy relies primarily on azoles, echinocandins, and amphotericin B. Azoles inhibit ergosterol synthesis and are broadly active against yeasts and moulds, although emerging resistance in non-albicans *Candida* and *Aspergillus* spp. limits their utility.[12] Echinocandins inhibit β-1,3-D-glucan synthesis and remain first-line treatments for candidaemia, but require intravenous administration and are susceptible to FKS-mediated resistance.[13] Amphotericin B retains potent fungicidal activity but is constrained by nephrotoxicity and the need for inpatient administration.

Recent advances have introduced several novel agents that address resistance, improve delivery, and broaden the spectrum of therapy. Ibrexafungerp, a triterpenoid glucan synthase inhibitor, is Food and Drug Administration (FDA)-approved for vulvovaginal candidiasis and demonstrates activity against echinocandin- and azole-resistant *Candida*, including *C. auris*.[14] Rezafungin, a next-generation echinocandin with a prolonged half-life, allows once-weekly intravenous dosing and achieved clinical cure rates comparable to standard therapy in the STRIVE phase 2 trial.[15] Fosmanogepix, a first-in-class inhibitor of the Gwt1 enzyme in glycosylphosphatidylinositol (GPI) anchor biosynthesis, achieved approximately 80% treatment success in invasive candidiasis, including in multidrug-resistant strains, with favourable tolerability.[16] Olorofim, the prototype orotomide targeting dihydroorotate dehydrogenase, has shown activity against azole-resistant *Aspergillus* spp. and other moulds, with six-week response rates of ~29% in refractory invasive mould disease.[17] Opelconazole, an inhaled triazole optimised for pulmonary delivery, is in late-phase trials for prophylaxis and treatment of pulmonary aspergillosis, aiming to minimise systemic exposure. Encochleated amphotericin B represents an oral polyene formulation that enhances bioavailability and reduces toxicity, potentially enabling outpatient treatment of candidiasis and cryptococcosis.[18]

Collectively, these agents expand oral and intravenous options, enable novel mechanisms of action, and support combination strategies for difficult-to-treat or resistant infections. Their development reflects a critical evolution in the antifungal pipeline, addressing gaps in safety, delivery, and efficacy that have limited traditional antifungal therapy for decades. **Table 1** summarises their indications, current versus future options, and key clinical considerations.[19]

Future directions

The rising global burden of invasive fungal infections necessitates a shift in antifungal strategy that extends beyond drug discovery alone. Future directions in antifungal therapy will require the integration of personalised medicine approaches, deliberate efforts to improve equitable access to essential antifungal agents, and the adoption of artificial intelligence (AI)-driven tools for surveillance and clinical management.

Personalised antifungal therapy is increasingly important due to marked variability in host factors, pathogen susceptibility, and

antifungal pharmacology. Azole antifungals remain foundational agents for both treatment and prophylaxis, yet their use is complicated by extensive drug–drug interactions and unpredictable pharmacokinetics. Most azoles inhibit cytochrome P450 enzymes, particularly CYP3A4 and CYP2C19, resulting in clinically significant interactions with immunosuppressants, chemotherapy agents, and antiretroviral therapies.[20] These interactions can lead to toxicity or inadequate antifungal exposure, both of which contribute to poor outcomes and selection of resistant strains. Therapeutic drug monitoring has therefore become an essential component of azole therapy, especially for voriconazole and posaconazole, and is likely to expand further as newer agents are incorporated into practice.[21]

In parallel, advances in pharmacogenomics and fungal molecular diagnostics are laying the groundwork for more precise antifungal selection and dosing. Rapid identification of fungal species and resistance-associated mutations enables earlier optimisation of therapy and may support individualised combination strategies for patients with refractory or multidrug-resistant infections.[22,23] As the antifungal armamentarium grows, personalised approaches that account for host immune status, site of infection, and pathogen genotype are expected to play an increasingly central role in clinical decision-making.[22,23]

Equitable access to antifungal therapies represents a critical and unresolved challenge. The COVID-19 pandemic highlighted profound global inequities in access to lifesaving vaccines, with low- and middle-income countries experiencing delayed and limited availability despite bearing a disproportionate disease burden.[24] A similar pattern exists for antifungal drugs. Access to liposomal amphotericin B, flucytosine, and newer antifungal agents remains limited in many regions with high incidence of cryptococcal meningitis, mucormycosis, and other invasive fungal infections.[25,26] Without co-ordinated global strategies addressing pricing, manufacturing, and procurement, advances in antifungal development risk exacerbating existing disparities rather than reducing fungal-related mortality.[26,27]

AI and digital health technologies offer promising opportunities to improve fungal disease surveillance and management. Machine

learning models have demonstrated utility in identifying patients at high risk for invasive fungal infections in intensive care populations.[28] Integration of electronic health record data, imaging, and microbiologic results may enable earlier diagnosis, targeted prophylaxis, and improved antifungal stewardship. At a population level, AI-driven surveillance systems could facilitate real-time monitoring of antifungal resistance and rapid detection of emerging threats such as *C. auris*, supporting more effective public health responses.[28,29]

Conclusion

Invasive fungal infections are a significant and growing global health threat, driven by immunocompromised populations, emerging multidrug-resistant pathogens such as *C. auris*, and environmental changes expanding endemic fungal ranges. Outbreaks, including COVID-19-associated mucormycosis, highlight the interplay of host susceptibility, healthcare factors, and pathogen characteristics. While traditional antifungal options remain limited, new agents with novel mechanisms, improved delivery, and broader spectra are expanding treatment possibilities. Advances in molecular diagnostics and personalised therapy enable more precise management, and integrated surveillance is essential to track emerging threats. These developments provide a foundation for addressing the rising burden of fungal disease worldwide.

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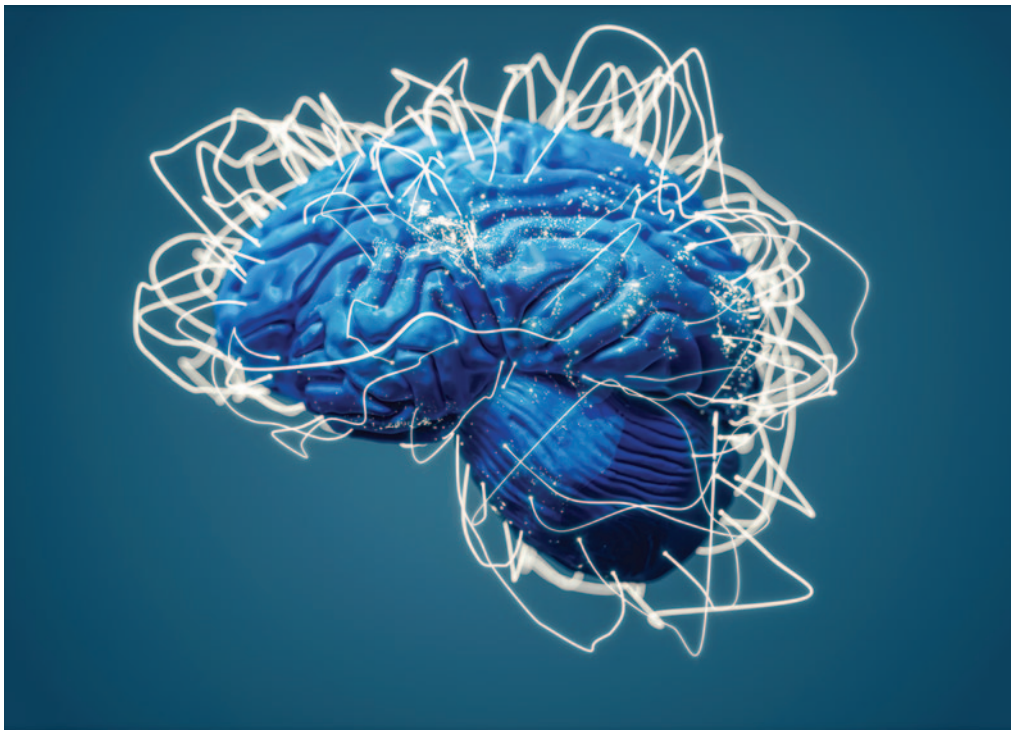
Mapping minds with machines: the promise and pitfalls of connectomic medicine



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Declaration of generative AI
During the preparation of this manuscript, the author(s) used generative artificial intelligence (GenAI) to assist, where applicable, with language editing, sentence refinement, and improvement of readability. All content generated or modified using these tools was carefully reviewed and verified by the author, who takes full responsibility for the integrity, accuracy, and originality of the work.

Abstract

Connectomics is a field centred around mapping the structural and functional connectivity of the brain. Traditionally, the brain has been thought of as having 52 distinct sections based on Brodmann's map; however, connectomics presents a more comprehensive understanding of neuroanatomy. The Human Connectome Project was a landmark study that analysed the brain's functional and structural connectivity. It divided the brain into 360 regions known as "parcels" based on distinct patterns of cortical architecture, functional activity, and connectivity. By utilising knowledge of the connectome, physicians are provided with greater understanding of psychiatric and neurological pathology, and can discern brain regions affected in psychiatric disorders such as major depressive disorder. This aids in diagnosis as well as monitoring responses to treatments. Furthermore, it enhances non-invasive measures such as transcranial magnetic stimulation for personalised treatment of disorders. Physicians are also granted more precise knowledge of important areas to avoid in neurosurgical planning, and improved understanding of the consequences of tumours in these regions. Emerging tools utilising artificial intelligence are being coupled with connectomic analysis to aid in psychiatric and neurosurgical use. This review presents an overview of the current state of connectomic medicine across neurosurgery and psychiatry, and limitations hindering widespread adoption.

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Introduction

Historically, the brain has been thought to be divided into 52 distinct areas based on Brodmann's map.[1] This 1909 map, while not incorrect compared to modern knowledge, is overly simplified and, importantly, lacks details on the intricate connectivity of the brain. In 2010, a five-year US$30m project was launched by the National Institutes of Health (NIH) called the Human Connectome Project (HCP), with the goal of revealing the connectivity of the human brain.[2,3] The HCP collected structural and functional brain data from over 1,200 healthy adults using advanced neuroimaging techniques to map the relationships between structural and functional connectivity of the brain.[4,5] Using this large dataset, they were able to localise brain networks to create a detailed group-level "connectome" that represents the brain's large-scale network architecture. The HCP divided the brain into 360 regions called "parcels" – 180 per hemisphere – compared to the 52 from Brodmann's map.[6] Unlike Brodmann's map, the "connectome" displays very detailed structural–functional connectivity between these various brain regions. It is thought of as a complete "point-to-point spatial connectivity of neural pathways in the brain".[7]

The connectome, though deeply intertwined, can be further divided into functional subunits. An example of this is the default motor network (DMN), which includes regions such as the ventromedial prefrontal cortex (vmPFC), posterior cingulate cortex (PCC), and posterior parietal cortex (PPC).[8-11] The DMN is mainly involved in internally oriented cognitive processes such as rumination and increased self-focus, as well as wakeful rest state activity.[12,13] Aligning with its functions, the DMN has been implicated in major depressive disorder (MDD), trapping patients in internally direct negative spirals. Structures such as the inferior parietal lobe and anterior frontomedial cortex are both part of this system, demonstrating how even anatomically distant parcels can have significant functional relationships, in contrast to Brodmann's map. The DMN is one of many functional networks in the brain. There are various others such as the salience network (SN) and central executive network (CEN). All of these networks have important functions and can be implicated in MDD, as well as in various conditions such as bipolar disorder and schizophrenia.[14,15]

The next step beyond identifying these regions is to translate this knowledge into meaningful clinical improvements. By leveraging our understanding of the human connectome, we can compare healthy brain networks to those of patients with various psychiatric conditions such as MDD.[14] This allows clinicians to determine which specific brain circuits may be dysfunctional and may help to guide non-invasive treatments. Additionally, connectomic insights can be used to optimise neurosurgical interventions, allowing surgeons to avoid disrupting critical functional tracts and potentially reducing the risk of postoperative neurological deficits.[16] This review provides an overview of the current clinical applications of connectomic medicine, discussing its applications in psychiatric and neurosurgical treatment, as well as current limitations hindering widespread implementation.

In 2010, a five-year US$30m project was launched by the National Institutes of Health (NIH) called the Human Connectome Project (HCP), with the goal of revealing the connectivity of the human brain.

Creating the connectome

Making a connectome marked a major milestone in our understanding of the complete wiring of the nervous system. This achievement became possible thanks to technological advancements in high-resolution neuroimaging. Magnetic resonance imaging (MRI) is foundational to building a macroscopic connectome. Two key techniques are MRI with diffusion-weighted imaging (DWI) and functional MRI (fMRI). DWI is a specialised MRI method that captures the movement of water molecules along white matter tracts, which are the communication pathways for nerves.[17] Water molecules move more easily along white matter fibres than across them, and this directional movement can be analysed using specialised algorithms, a process known as tractography, to create detailed models of the brain's structural wiring.[17,18] In contrast, fMRI measures brain activity by detecting changes in blood oxygenation between regions.[19] When regions are more active, they display higher levels of blood flow. This allows researchers to map functional connectivity between various areas of the brain based on how strong their fMRI activity is.[20] Furthermore, fMRI analysis can be divided into task-based fMRI (tb-fMRI) and resting-state fMRI (rs-fMRI). Tb-fMRI measures brain activity during specific tasks to identify functionally engaged regions, while rs-fMRI captures spontaneous activity when the subject is at rest.[21] Together, these approaches allow detection of intrinsic network alterations at baseline that are associated with psychiatric conditions, as well as identification of task-specific networks engaged during cognitive processes. Together, these tools, along with DWI, helped to reveal the brain's structural and functional connectomes, which were subsequently parcellated into 180 regions per hemisphere based on distinct patterns of cortical architecture, functional activity, and connectivity.[6]

Planning procedures

Although still a fairly novel research method, using DWI with tractography helps neurosurgeons to avoid key functional pathways in the brain, as well as to view relations of tumours to these tracts.[22] The use of connectomics may allow neurosurgeons to tailor approaches that are least invasive to vital networks in the brain.[22] Switching to a connectome-based approach may allow for recovery after surgical intervention in areas once thought of as inoperable due to risk of damaging "eloquent" structures.[16]

Eloquent structures have been defined as inflexible brain regions, including areas involved in sensorimotor, language, and visual cortices, regions that would result in significant cognitive impairment if damaged.[16] Specific functions such as language were thought to be precisely correlated with specific locations such as Broca's and Wernicke's areas.[23,24] Connectomics has challenged this localisationist theory, demonstrating language involvement in many areas beyond Broca's and Wernicke's areas, such as the frontotemporoparietal network, the basal ganglia, cerebellum, and many others.[23] This new understanding has allowed for tumour resections in "eloquent" areas, enabling preoperative planning tailored to the patient's individual brain networks. Such approaches aim to maximise the extent of resection while preserving social, cognitive, and emotional functions.[16]

Understanding brain tumours

Connectomic medicine has also shifted the way we view and approach resections of lesions in the brain. For instance, meningiomas and metastases usually occur as focal lesions, which suggests focal involvement, but have been found to disrupt brain networks through raised intracranial pressure and oedema, potentially creating system-wide effects.[25] Oedema increases pressure, subsequently inducing local hypoxia. This causes subsequent damage to white matter tracts, which can lead to disruption of distant brain regions.[25] This aligns with clinical findings, as peritumoural oedema has been found to be significantly associated with lower scores on cognitive testing, which can improve after resection in meningiomas.[25]

Making a connectome marked a major milestone in our understanding of the complete wiring of the nervous system. This achievement became possible thanks to technological advancements in high-resolution neuroimaging.

In contrast to the indirect pressures of meningiomas and metastases, diffuse gliomas have been found to directly infiltrate brain tissue along white matter pathways.[25] This leads to disturbed functional connectivity beyond the expected anatomic margins of the tumour.[25] In diffuse gliomas, it has been shown that functionally connected regions tend to have the greatest connectivity lost even if the region is not directly adjacent to the tumour.[25] These findings of functional connectivity translate into clinical outcomes. In a prospective study of 117 glioblastoma patients, Wei *et al.* found this widespread dysfunction to be significantly associated with cognitive impairment, preoperative cognitive performance, and overall survival.[26]

Additionally, using knowledge of tumours and the connectome, surgeons may be able to use emerging artificial intelligence (AI) tools to aid operations and prognosis. With the help of an AI

neuronavigation software based on the HCP to visualise important brain networks, Yeung *et al.* predicted postoperative neurologic deficits in 15 patients undergoing high-risk craniotomies.[27] In eight patients where deficit occurred, the software predicted it – except for one occurring from a postoperative stroke.[27]

Furthermore, using software allows surgeons a more nuanced approach to navigate key regions involved in language.[28] This was demonstrated in the case of two patients with high-risk lesions near language networks. Both patients showed intact or improved language at follow-up despite the surgeon having to navigate Broca's area, a key eloquent region for speech.[28,29]

These studies collectively demonstrate the vast amount of oncological knowledge gained from connectomic medicine. Utilising the connectome has also provided promising outcomes in neurosurgical interventions; however, more studies are needed in this field.

Connectomic medicine has also shifted the way we view and approach resections of lesions in the brain.

Connectomics in psychiatry

Connectomics has revolutionised the way we understand and can treat MDD and other psychiatric conditions. Using knowledge of the connectome, we can now understand which areas of the brain are not functioning properly in MDD. For instance, the DMN is responsible for many cognitive processes connected to the symptoms of MDD, such as rumination and increased internal focus.[12,30] Altered functional connectivity of the DMN has been found to be significantly associated with MDD.[31] This makes sense when remembering its functions of internal self-processing – it has the potential to trap an individual in negative ruminations relating to the past and future, and potentially create a negative self-image when functioning improperly.

AI tools can also be implemented to aid diagnoses based on connectome data – not just in MDD patients. For instance, machine learning data have been able to identify patients with autism spectrum disorder, with accuracies ranging from 64% to 94%.[32] Furthermore, a systematic review found that multiple deep learning models were able to diagnose schizophrenia, with accuracies above 80%.[33]

Connectome-based approaches can provide a better understanding for psychiatric diagnoses by identifying network-level alterations, as well as potentially supporting the development of personalised treatments and evaluating treatment responses in patients.

Transcranial magnetic stimulation

Understanding connectome dysfunction in psychiatry is particularly useful when employing non-invasive therapies such as transcranial magnetic stimulation (TMS). Pioneered by Barker *et al.* in 1985, TMS uses a rapidly changing magnetic field to stimulate specific areas of the cerebral cortex through the scalp.[34,35] This is achieved by placing a magnetic coil over the scalp, which creates a magnetic field that passes through the skull and creates an electric current in the brain.[36] The cerebral cortex conducts this energy into neurons, leading to depolarisation.[35] This neuronal depolarisation can result in both behavioural and physiological changes, depending on the brain region targeted.[36]

Connectomics has revolutionised the way we understand and can treat MDD and other psychiatric conditions. Using knowledge of the connectome, we can now understand which areas of the brain are not functioning properly in MDD.

Initially, TMS was developed as a single-pulse technique to explore brain function, and has developed into repetitive TMS (rTMS) to deliver repeated magnetic pulses over time to alleviate symptoms and normalise abnormal brain activity in various psychiatric conditions.[37] Further expanding rTMS, connectome guidance has massive potential to guide individualised therapy.

Traditionally, rTMS therapy would target regions of the brain such as the dorsolateral prefrontal cortex (DLPFC).[38] Variations in response to treatment are known to occur and this may be due to the heterogeneity of regions like the DLPFC, with the HCP dividing it into 13 different regions of interest.[39] More specific treatment targeting based on parcels may be able to improve outcomes and create more consistent responses. In a proof of concept study, Tang *et al.* demonstrated significant improvement in quality of life in a cohort of MDD patients using personalised rTMS.[39]

rTMS has been invaluable for treatment of many conditions and they may be greatly supplemented using individualised connectomic guidance; however, more research in this area is warranted.

Limitations of connectomics

Despite the groundbreaking implications of connectomic medicine, and the value it has already provided, there remain limitations hindering its widespread adoption. Reproducibility errors have been reported, with variability in rs-fMRI scans across multiple points in time in patients, which are compounded by varying imaging protocols among studies.[25,40] Further hindering

reproducibility, connectome mapping software has been noted to interpret connectome data with variability.[28] Additionally, when used on differing ethnicities, particularly minorities, deep learning models on connectome data have greater difficulties.[41] Datasets such as the HCP may have insufficient inclusion of minorities such as African Americans to develop reliable models for their use.[41] Another issue with connectomic clinical applications is that many studies have low sample sizes and are still experimental.[25,42] This creates a need for prospective validation on the use of these tools by larger cohort studies. With improvements in methodology and greater standardisation, the usage and indications for connectomic tools are likely to increase as future studies continue to validate current findings.

Conclusion

Although still in its early stages, connectomics has greatly enhanced our understanding of neural networks. This has provided numerous benefits, including improved psychiatric diagnosis, guidance for neurosurgical interventions, and support for non-invasive techniques such as rTMS. Connectomics is expected to make an even greater impact in medicine as larger prospective studies validate current findings, and as AI tools continue to be integrated.

Although still in its early stages, connectomics has greatly enhanced our understanding of neural networks.

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The role of obstetrics, gynaecology and fertility medicine in caring for transmasculine and gender diverse people

Abstract

Transgender and gender diverse (TGD) people have unique obstetric and gynaecological needs. This review explores considerations for providing obstetric and gynaecological care to the TGD population. It is important that cervical cancer screening for TGD people is guided by trauma-informed care principles, as they are at high risk of adverse healthcare experiences. Screening for breast and endometrial cancers in TGD people who are assigned female at birth is recommended to follow the same guidelines as those for cisgender women, if breasts and/or uterus are retained. Transmasculine (TM) individuals may experience infertility issues after beginning gender-affirming hormone therapy (such as exogenous testosterone) and should receive counselling on these before commencing such regimes. Fertility preservation methods such as oocyte retrieval and cryopreserving oocytes should be discussed. TM individuals are also at risk of pregnancy if having sexual intercourse with a sperm-producing partner(s). Pregnancy prevention options should be discussed if the person does not wish to become pregnant. If considering pregnancy, TM individuals should discuss terminating testosterone hormone therapy before conception with a healthcare professional.

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Table 1: Glossary of terms relevant to gender diversity.

Terminology	
Transgender and gender diverse (TGD)	People whose gender identities or expression are different from the gender ascribed to the sex designated at birth[1]
Transmasculine (TM) individuals	People who have a masculine spectrum gender identity, with female listed as the sex on their birth certificate. This is inclusive of, but not limited to, transgender men, transmasculine people, non-binary people, and other gender-diverse people designated female at birth[4]
Gender-affirming care (GAC)	Social, medical, legal, behavioural, or a combination of processes recognising or affirming TGD people in their gender identity[1,9]
Gender incongruence (previously gender dysphoria)	Distress that accompanies the incongruence between a person's experienced gender and the sex designated at birth[51]
Gender-affirming hormone therapy (GAHT)	Masculinising or feminising hormone therapy through administration of exogenous endocrine drugs[52]

Introduction

Transgender and gender diverse (TGD) people are individuals whose gender identities/expressions are different from the gender ascribed to their sex assigned at birth.[1] Although data surrounding the prevalence of TGD people are limited, it is estimated that 0.8% of adults and 3.3% of youths between 13 and 17 identify as TGD in the United States.[2] TGD people face significant barriers to accessing healthcare, which may partly reflect gaps in healthcare provider (HCP) experience and training.[3] Many barriers stem from discrimination and variability in provider knowledge and comfort, which may contribute to gaps in care. These challenges may lead to reduced access to and underuse of healthcare services.[4]

Family doctors and obstetrician-gynaecologists (OBGYNs) are among the first points of contact for TGD people within the healthcare system.[5] Therefore, it is vital that OBGYNs have sufficient knowledge and awareness to provide appropriate and inclusive treatment for TGD people. TGD people also experience disproportionately high rates of childhood trauma and adverse childhood experiences.[6] This is especially relevant in OBGYN settings, where encounters may involve highly sensitive examinations and discussions that risk reproducing prior trauma.[7] Given the combined impact of healthcare barriers, high prevalence of trauma, and adverse healthcare experiences, greater emphasis on trauma-informed, inclusive practices is needed.[7] Increased awareness, identification and treatment of the unique OBGYN healthcare needs of the TGD community are also needed, particularly for transmasculine (TM) individuals.

The objective of this article is to explore considerations in the provision of OBGYN care for TM individuals. Specifically, this review will focus on cervical, ovarian and breast cancer screening, contraception, pregnancy prevention and termination, and fertility and pregnancy options relevant to TM individuals. Given the diverse healthcare needs of TGD people, the scope of this review will be limited to TM individuals, defined as people who partially or fully identify as masculine, with female sex at birth.[4] This includes transgender men and other TGD people designated female at birth.[8]

Cervical cancer screening and trauma-informed care

Gender affirming care (GAC) refers to practices that recognise or affirm TGD individuals' gender identity through social, medical, legal, or combined approaches.[1,9] Medical GAC for TM individuals often involves exogenous testosterone to cause masculinising effects.[10] Masculinising gender-affirming surgeries encompass a range of procedures, guided by patient–provider conversations, rather than a single standardised surgery.[11] Many TM individuals retain a cervix and therefore remain at risk of cervical cancer.[12]

Despite this risk, limited data exist on cervical cancer prevalence in TM populations, and the burden of human papillomavirus (HPV) infection and HPV-related cancer in this group is largely undocumented.[13] TM people demonstrate lower rates of cervical cancer screening, which may place them at greater risk when compared to cisgender women, even when HPV prevalence is similar.[14,15] For those who have not received the HPV vaccine, counselling and vaccination should be discussed.[16] TGD people with a cervix are less likely to undergo conventional cervical cancer screening, often due to the potential for examinations to worsen gender incongruence and/or because of HCP and patient misconceptions regarding the need for screening.[17,18]

This gap is compounded by the lack of specific cervical cancer screening guidelines for TGD people from major bodies such as the American Cancer Society and the US Preventive Services Task Force.[19-21] Similarly, the World Health Organization International Agency for Research on Cancer does not provide TGD-specific screening guidelines, beyond noting that transgender men are less

likely to be screened.[22] In contrast, both the American College of Obstetricians and Gynecologists (ACOG) and the World Professional Association for Transgender Healthcare (WPATH) Standards of Care for the Health of Transgender and Gender Diverse People Version 8 recommend that TGD people who currently have, or previously had, a cervix, be offered cervical cancer screening in accordance with local guidelines for cisgender women.[1,4] WPATH also notes the lack of research on cervical and breast cancer screening in TM populations.[1]

TM people can also miss cervical screening and other sexual health services because they may not be consistently included in the target lists for screening invites.[13] Many report negative experiences related to HCP insensitivity or limited knowledge of TGD health issues.[7,19,23,24] Gender incongruence, prior sexual trauma, mistrust of HCPs, and healthcare-related anxiety can also lead to complete avoidance of cervical cancer screening.[19,25] Notably, Carroll *et al.* found that among TGD people who delayed cervical cancer screening, 30% did so due to concerns about potential mistreatment related to their gender identity.[24]

HCPs can help to mitigate these barriers by adopting sensitive, inclusive, and respectful approaches to TGD care. This can be accomplished by further education on the best practices for TGD healthcare and principles of trauma-informed care.[7,19,26,27] Trauma-informed care is a central component of high-quality healthcare, emphasising patient autonomy, respect, cultural sensitivity, and empowerment.[28] Practical strategies include asking for and consistently using a patient's preferred name, pronouns, and terminology.[29] When medically relevant, asking and using the patient's preferred anatomical terminology can help to foster a safe and supportive environment, as some may find gendered terminology uncomfortable.[17] When preferences are unclear, gender-inclusive/gender-neutral language may be used, and offering the option of bringing a support person can be helpful.[16]

It is important that HCPs are mindful of performing pelvic speculum examinations in a way that minimises pain and distress, and adopt trauma-informed care principles. HCPs are advised to be mindful that a TGD person may have experienced past trauma during a pelvic exam, and to let the patient decide if and when to continue with, or to stop the exam.[17] When speculum examinations are not feasible, alternative approaches such as blind Pap or HPV testing may be considered and, depending on patient risk factors, may satisfy screening requirements.[16]

Ovarian and breast cancer screening

The effects of exogenous testosterone on the formation and growth of ovarian cysts remain relatively unknown. However, TM people on testosterone are at risk of developing cystic ovaries.[30] This can result in pain syndromes and necessitate clinical evaluation and management.[16] For ovarian and endometrial cancer, WPATH recommends that HCPs screen TGD people according to the same screening guidelines developed for cisgender women.[1] Current consensus guidelines do not recommend routine ovarian cancer screening for cisgender women, and this recommendation extends to TGD populations.[31]

A systematic review by Joint *et al.* found insufficient evidence to estimate breast cancer prevalence in the TGD population.[32] Although there is some evidence that gender-affirming hormone therapy (GAHT) does not increase the risk of breast or reproductive cancer, further well-designed studies are needed to confirm these findings.[32,33] Regardless of gender identity, any anatomic organ that meets criteria for screening should be evaluated appropriately.[29] However, there are currently no established cancer screening guidelines, recommendations, or protocols specific to TGD patients.[33]

Pregnancy prevention and termination services

Although exogenous testosterone can stop menstruation, some TM people may still menstruate. Bleeding beyond six months of testosterone therapy, while uncommon, may reflect breakthrough ovulatory events or endometrial atrophy.[34] Reported rates of contraception use among TM people vary widely, with rates ranging from 20-60%.[35-37] Some TM patients may not use contraception due to the assumption that testosterone is a reliable form of contraception.[1,36,38,39] However, testosterone should not be considered a reliable form of contraception, as it does not completely suppress the hypothalamic-pituitary-adrenal axis.[1,40]

While testosterone may affect reproductive capacity, many TM people may retain fertility and should be counselled about the risk of unplanned pregnancy.[29,35] Assessment of sex practices is a priority, as there is large variation across patients.[16] It is important that TGD people have access to safe, legal, and gender-affirming termination procedures for unplanned or unwanted pregnancies.[1] Pregnancy counselling should also be readily available.

WPATH's Standards of Care highlight a profound gap in research on how GAHT, such as exogenous testosterone regimes, affects hormonal contraceptive efficacy or safety.[1] Currently, no studies have examined how testosterone GAHT regimes influence the effectiveness or risk profile of hormonal contraceptives, including combined oestrogen-progestin and progestin-only methods, or non-hormonal and barrier methods such as condoms, non-hormonal intrauterine devices, and diaphragms.[1]

Fertility options alongside gender-affirming care

Studies show that approximately half of TGD people express the desire to have children in the future, a proportion comparable to that of cisgender people.[2] Some TGD individuals wish to have genetically related children, including the option of carrying a pregnancy and giving birth.[41] For individuals considering gender-affirming hormonal care, discussions surrounding fertility and parenting options should be considered early in the process, ideally before the initiation of GAHT or gender-affirming surgery.[29] This is because GAHT and gender-affirming surgery can alter reproductive anatomy or function, and may limit future reproductive options.[1,42,43]

The current literature raises more concerns than answers regarding best practice for fertility preservation and/or treatment in TM individuals.[44] WPATH's Standard of Care recommends informing TGD people of the reproductive impact of GAHT, including the potential loss of fertility, and discussing available fertility-preserving options. However, WPATH provides limited guidance on fertility options for those who have already commenced GAHT.[1] As such, it is critical to discuss infertility risk and fertility preservation options with TGD individuals and their families, prior to initiating GAHT or surgical interventions, and to continue these conversations longitudinally as care evolves.

Technologies such as oocyte retrieval and cryopreserving oocytes may be offered to TM patients.[42] However, the medications and procedures for cryopreserving oocytes (e.g., pelvic examination, vaginal ultrasound monitoring, and oocyte retrieval) may lead to increasing gender incongruence.[45] Assisted reproductive technologies should therefore be discussed with sensitivity, and ideally before starting GAHT, as aspects of the fertility preservation process may intensify gender incongruence.[45,46]

Pregnancy options

TGD people can and do achieve parenthood through pregnancy.[41] Most TM people retain their uterus and ovaries, and may therefore conceive and carry a pregnancy, even after long-term testosterone use.[16,35] Although case reports describe TM people who have successfully carried pregnancies and given birth, few prospective studies have assessed the impact of long-term GAHT on fertility.[1,35,47] Since stopping gender-affirming hormones may cause distress and exacerbate gender incongruence, decisions regarding when and how to pause therapy should be discussed during prenatal counselling.[48]

If a TGD person conceives while taking testosterone, they should be advised to stop taking it if they plan to continue with the pregnancy. After the long-term use of testosterone, conception and successful pregnancy can occur;[29] however, the optimal timing for the discontinuation of testosterone prior to pregnancy and resumption postpartum is unknown.[1] For some TM people, the prospect of stopping testosterone itself can provoke feelings of severe discomfort.[1] Exogenous testosterone poses potential risks during pregnancy, as it is classified as a teratogen and can cause virilisation of female foetuses.[1,34] Accordingly, WPATH recommends discontinuing testosterone or masculinising hormone therapy prior to conception and throughout pregnancy.[1] Despite these recommendations, there is a lack of data on the relationship between duration of testosterone exposure and the risk of teratogenicity. No consensus has established the ideal timing of testosterone cessation before attempting pregnancy. Albar *et al.* found that, among TM patients who had recently started on testosterone and were undergoing assisted reproductive technologies, the timing of stopping testosterone was not associated with the number of mature oocytes retrieved.[49] Few studies have examined ovulation during treatment with injected testosterone. Taub *et al.* suggest that testosterone rapidly supresses the hypothalamic-pituitary-gonadal axis, leading to anovulation in a proportion of new users.[34] However, some long-term testosterone users break through the hormonal suppression and undergo ovulation.[34] Overall, existing data suggest that while exogenous testosterone commonly suppresses ovulation, its long-term impacts remain incompletely characterised.

Care should remain patient centred and individualised, with attention to each person's parenthood goals. Pregnancy and family planning options for the TGD individual ultimately depend on factors such as their partner's reproductive anatomy, relationship status, and willingness or ability to carry a baby, similar to considerations faced by any person seeking assisted reproductive technologies for current or future fertility.[50]

Conclusion

TGD people are a diverse population with unique healthcare needs. Cervical cancer screening should be offered to TGD people with cervixes and should follow trauma-informed care approaches. WPATH recommends that counselling regarding future fertility issues and fertility preservation options should be offered before commencing GAHT. TM individuals taking testosterone may become pregnant when engaging in sexual activity with sperm-producing partners, and should be made aware of this and offered appropriate contraception advice. If wishing to carry a pregnancy, WPATH recommends that TM patients terminate testosterone use before conceiving. Since the duration of testosterone cessation prior to conceiving is largely unstudied, those wishing to carry a pregnancy should be advised on pausing GAHT during pre-conception and pregnancy.

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Women and burn healing: the role of oestrogen and societal influence on cause, treatment and prognosis

Abstract

This article examines burn healing from a sex- and gender-specific perspective. Burn injuries remain a major global health challenge, with evidence suggesting that women are more severely affected than men. Despite progress in the available research, the underlying hormonal influences on the burn healing process remain poorly understood. Examining the effect of oestrogen, as focused on in this review, could offer a new perspective on the burn healing process and potential treatment options. Furthermore, gender discrimination plays a role in burn prevalence and prognosis, as women globally are more likely to suffer from burn injuries and to receive chemical burns as a result of gender-based violence, but are less likely to receive surgical intervention than men. This review examines the underlying biological mechanisms that distinguish burn/non-burn repair. It will try to establish, based on available literature, whether oestrogen has any effect on burn healing. Additionally, understanding the influence of gender discrimination on burn rates and prognosis can convey the true burden of burn injuries experienced by women worldwide. Future research on this topic should explore the effects of oestrogen on burn healing, and whether exogenous oestrogen could be used to improve treatment and prevent complications.

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Introduction

Throughout human history, burns have occurred as a common form of trauma, thus prompting the development of medicinal remedies. The earliest documented treatment, dating to 1600 BC, is credited to the Egyptian Edwin Smith Papyrus, who proposed the use of honey and resin as a salve to soothe and protect burns.[1] Therapeutic strategies have evolved alongside the scientific community's understanding of burn healing, allowing more favourable patient outcomes.[2]

A growing body of research suggests that biological sex has a unique influence on wound healing. Oestrogen, the focus of this review, has been shown to accelerate inflammation, proliferation, and remodelling of dermal tissues, providing protective effects on wound healing.[3] While burns and non-burn wounds follow largely the same healing process, burns are characterised by features such as a prolonged systemic inflammatory response, providing a context in which the effects of oestrogen could be important. While hormonal influences contribute to sexual dimorphism in healing responses, the mechanisms underlying sex-specific differences in healing need to be studied further.[4] Clarifying these protective pathways, and understanding when or why they fail, could drive new therapeutic targets. Investigating both the effect of menopause on burn healing, and the potential role of hormone replacement therapy (HRT), could open discussions regarding the role of exogenous oestrogen in improving burn healing.

Throughout human history, burns have occurred as a common form of trauma, thus prompting the development of medicinal remedies.

Burn injuries disproportionately affect people in low- and middle-income countries (LMICs), who account for approximately 95% of the global burden.[5] Burns are a major contributor to long-term morbidity, and rank among the leading causes of disability-adjusted life years lost in LMICs,[6] accounting for approximately 180,000 deaths annually.[7] Gender-based disparities in burn injury epidemiology and outcomes persist across national income levels, with women experiencing more frequent and severe burns than men.[5] Women in LMICs are particularly vulnerable as they are more often exposed to burn injury hazards, many of these in and around the household related to cooking and heating.[6] Gender bias has been shown to impact the levels of treatment provided and the survival rates of burn victims admitted to hospitals, with female burn patients less likely to receive surgical treatment and more likely to die post hospitalisation than their male counterparts.[5] Additionally, women are more likely to be victims of chemical burns related to gender-based violence.[8] Improved understanding of both gendered and biological sex-specific factors influencing burn epidemiology and prognosis may aid in improving suboptimal outcomes across all, but especially more vulnerable, populations.[9]

This review aims to highlight the influence of female sex on burn healing, with a particular focus on the effects of oestrogen. Combining biological mechanisms with the influence of gender-based inequities on burn risk and prognosis provides a broader picture of the burden of burn injuries experienced by women worldwide.

This review aims to highlight the influence of female sex on burn healing, with a particular focus on the effects of oestrogen.

Overview of wound healing in burn and non-burn injuries

In non-burn traumas, the healing process typically progresses through four distinct phases: haemostasis; inflammation; proliferation; and, remodelling.[10] Following injury, the haemostatic phase initiates vasoconstriction to promote the aggregation of platelets and lymphatic components, leading to clot formation.[11] Inflammation follows closely behind, releasing cytokines and chemokines to facilitate collagen breakdown and fibroblast activation.[12] By days five to seven, the proliferation phase commences, leading to keratinocyte migration and angiogenesis to allow for wound contraction. After two weeks, the remodelling phase allows for the reorganisation of extracellular matrix components (such as oestrogen) to enhance the tensile strength of the repaired injury. Depending on the amount of trauma, this final stage can last from weeks to months.[13]

Although non-burn and burn wound healing may follow the same fundamental phases, there are notable differences in their progression and prognosis.[14] Burns will often lead to more extensive tissue damage depending on their depth – often affecting the dermis and underlying structures.[15] As a result, there is a prolonged systemic inflammatory response that ultimately delays healing and can lead to further complications,[16] such as the formation of hypertrophic scars.[17,18] Thermal injury can also destroy skin appendages (such as hair follicles and sweat glands),[19] which are important sources of epithelial cells for re-epithelialisation.[20] These wounds are also associated with a prolonged hypermetabolic response, with resting energy expenditure up to 180% above normal values – far more

severe than other forms of trauma.[21] These metabolic derangements can prevent full rehabilitation for burn survivors, due to resulting multi-organ dysfunction, whole body catabolism, changes in glucose metabolism, and sepsis.[22]

In non-burn traumas, the healing process typically progresses through four distinct phases: haemostasis; inflammation; proliferation; and, remodelling.

Oestrogen's effect on burn healing

Oestrogen is a primarily female-associated sex hormone that plays an important role in the development of female secondary sexual characteristics and the menstrual cycle.[23] Oestrogen additionally has systemic effects on the cardiovascular system,[24] brain function,[25] and skin health.[26]

One interesting yet understudied role of oestrogen is its effect on wound healing, more specifically, its context-dependent inflammatory and anti-inflammatory effects. In non-burn wounds, oestrogen has been associated with enhanced healing through the modulation of pro-inflammatory mediators such as macrophage migration inhibitory factor (MIF),[27] tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6).[28] The downregulation of these cytokines shortens the inflammatory phase.[28] Additionally, oestrogen increases fibroblast activity and extracellular matrix production,[29] including the deposition of collagen, which is critical for wound strength and structural integrity.[30] Thus, progression into the proliferative and remodelling phases of healing is accelerated, reducing scarring and hyperpigmentation,[31] two noted complications of burns.[32]

Although non-burn and burn wound healing may follow the same fundamental phases, there are notable differences in their progression and prognosis.

The benefits of topical oestrogen in cutaneous wound healing are widely accepted.[33] A logical cause of this is the role of oestrogen in increasing the late-stage transforming growth factor-beta 1 (TGF β1) signalling pathway by dermal fibroblasts.[34]

While there is little research specifically focusing on the relationship between oestrogen and burn healing, our knowledge of its effect on generalised cutaneous wound healing suggests a beneficial one. Considering the unique challenges faced in burn healing from the

extensive tissue damage and prolonged inflammatory response, oestrogen's ability to combat both of these could offer hope of potential use in treatment. However, this also creates questions regarding vulnerability in burn victims experiencing oestrogen deficiency. An example of this would be those experiencing menopause, a demographic where in recent years, the detrimental effects of this deficiency on healing is being increasingly researched.[35]

Menopause, exogenous oestrogen and burn healing

Menopause, typically starting between the ages of 45 and 55,[36] results in females living approximately one-third of their life in a state of systemic oestrogen deficiency.[37] Given the influence of oestrogen on burn healing, it could be hypothesised that this hormonal deficiency could adversely affect burn healing, the way it does in non-burn cutaneous wound healing, which slows down considerably during menopause.[38] This also poses the question of whether HRT, typically used to alleviate the symptoms of menopause,[39] could be used to modify burn recovery.

Population studies have linked burn injuries with an increased long-term risk of systemic conditions,[40] including diabetes, musculoskeletal disorders, infections, anxiety and depression.[41] Emerging evidence suggests that exogenous oestrogen may influence post-burn outcomes; however, it remains unclear whether the observed effects relate specifically to burn recovery or reflect broader systemic effects of oestrogen therapy (OT) in postmenopausal populations.[42] A 2023 observational study by Song *et al.* reported that postmenopausal women who suffered a burn injury were found to have lower rates of acute kidney injury post burn if they were on OT.[42] However, these patients experienced higher rates of myocardial infarction (MI), osteoporosis

and chronic kidney disease (CKD) up to three years post burn injury.[42] These inconsistencies suggest a need for further research into specific dosage and duration of treatment, both of which were low in this study.[42]

Another retrospective cohort study by Song *et al.* examined the effects of OT in postmenopausal women who sustained a mild burn injury within 10 years of beginning menopause. The study compared outcomes between women who received OT and those who did not, with the OT group defined as having initiated treatment at least six months prior to injury and continuing OT after burn injury. Within this burn-injured population, OT use was associated with lower rates of acute kidney injury, cerebral infarction, and sepsis three months after burn injury.[43] At three-year follow-up, OT was also associated with improved hypertrophic scarring in patients with burns of size greater than 20% of total body surface area (TBSA).[43] However, these findings are based upon observational data, and the OT dosage and regimen was not specified. Further research is required to determine the optimal timing, dosing, and extent of benefit of OT in burn recovery.

Considering the unique challenges faced in burn healing from extensive tissue damage and prolonged inflammatory response, oestrogen's ability to combat both of these could offer hope of potential use in treatment.

Any positive influences found from the use of exogenous oestrogen could potentially be used to improve poor burn treatment outcomes in the elderly female population, as elderly burn patients tend to lag behind their younger peers in mortality and successful recovery.[44]

Gender, intersectional identities and burn healing

Although biological sex may mechanistically affect burn healing, acknowledging the underlying social determinants that dictate the treatment of a female body are crucial in gaining a more holistic perspective of patient outcomes. A person's limited resources can have clinical consequences, with factors such as financial status, and access to healthcare, education and housing being contributing factors that shape both acute and long-term healing.[45]

Globally, women and girls are more likely to experience poverty than men and boys.[46] Financial disparity has been directly linked to poorer clinical outcomes post burn injury, including high rates of complications such as graft loss and readmission.[47] In a study examining socioeconomic status (SES) and healing outcomes in burns, individuals with a lower SES were five times more likely to experience graft loss than those of higher SES. Furthermore, evidence also shows that children whose families had a median income of less than $20,000 were 8.1 times more likely to sustain burn injuries than children from families with median incomes of more than $80,000.[47] These disproportionate findings are likely driven by the intersection of environmental and systemic factors. Populations with a lower SES often have fewer resources to support an optimal burn healing environment, and thus limited exposure to healing interventions.[48] These economic barriers exacerbate the injury and, ultimately, impair recovery rates.

Although biological sex may mechanistically affect burn healing, acknowledging the underlying social determinants that dictate the treatment of a female body are crucial in gaining a more holistic perspective of patient outcomes.

Gender discrimination also contributes to the risk of burn injury and healing. According to the World Health Organization (WHO) Global Burn Registry, women and girls are more likely to be exposed to burn injury hazards in LMICs.[5] This phenomenon can be attributed to gendered divisions of labour (such as domestic cooking) increasing exposure to open flames or scalds with flammable clothing or material.[6] Long-term recovery is also affected as female burn survivors report poorer health-related quality of life and are less likely to receive surgical treatment, despite experiencing more severe burns.[5] A 2021 WHO Global Burn Registry Cohort Study found that female burn patients were less likely to receive surgical treatment than male patients (49% vs 56%) and were more likely to die in hospital (26% vs 16%).[5] Additionally, women are more likely to be victims of intentional burns than men, typically because of gender-based violence.[8] A comparative study from Nepal found that patients hospitalised from intentional burns are more likely to be female, that the burns are typically larger (55% vs 25% TBSA), and that the patients are more likely to die than those with unintentional burns.[49]

Lower-income populations often face greater exposure to unsafe living conditions, reduced access to timely and specialised burn care, and fewer resources to support optimal wound management and rehabilitation.[49] Economic barriers may also limit engagement with

long-term follow-up, physical therapy, and scar management, thereby exacerbating functional impairment and prolonging recovery. Together, these findings highlight the critical role of socioeconomic inequality in shaping both the risk of burn injury and the quality of healing outcomes, underscoring the need for structural interventions alongside clinical advances.

According to the World Health Organization (WHO) Global Burn Registry, women and girls are more likely to be exposed to burn injury hazards in LMICs.

Conclusion

Burn healing is ultimately a multifaceted process, the intersection of both biological and social factors. Hormones such as oestrogen can influence pro- and anti-inflammatory immune responses and tissue repair, while the social determinants of health, such as gender, affect external exposure and rehabilitation. Understanding the interplay between these factors is crucial in examining the gender disparities in mortality and potential sequelae for burn patients. Future research should further study the influence of oestrogen on burn healing over general wound healing. The effect of pregnancy-level hormones on burn injury recovery could be explored, as well as the future role of HRTs such as exogenous oestrogen in improving outcomes for burn patients. A vested interest in this research is needed to ensure that the historic neglect shown to the global gendered and sex-specific causes of these injuries is appropriately addressed.

Burn healing is ultimately a multifaceted process, the intersection of both biological and social factors.

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The neurobiology of suicide: how the brain overrides survival instincts

Abstract

Suicide is a leading cause of preventable death across all age groups globally. Severe emotional trauma and pathophysiological neurological changes contribute to suicide by eroding basic survival mechanisms. This article reviews the neurobiological changes that erode survival instincts, with a focus on alterations in brain structures, stress-response systems and neurotransmitter functions associated with suicidality. Primary sources used were peer-reviewed narrative and systematic reviews, which integrated evidence from human postmortem studies, neuroimaging research and neurochemical analyses. Across these modalities, individuals who have attempted or died by suicide show structural and functional brain abnormalities. Most studies report reduced grey matter volume in areas regulating stress and impulse control, particularly the prefrontal cortex and amygdala. Disrupted connectivity between these regions further compromises impulse control and heightens emotional dysregulation. These structural changes are coupled with dysregulation of the hypothalamic-pituitary-adrenal axis, leading to unchecked stress responses. Serotonergic deficits also hinder mood regulation. Together, these processes undermine the neural mechanisms that prevent self-harm, underscoring suicide as a multifaceted phenomenon arising from the interaction of emotional trauma and physiological dysfunction. Understanding these mechanisms may allow for better-informed strategies for risk identification, prevention and intervention.

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Declaration of generative AI

During the preparation of this manuscript, the author(s) used generative artificial intelligence (GenAI) to assist, where applicable, with language editing, sentence refinement, and improvement of readability. All content generated or modified using these tools was carefully reviewed and verified by the author, who takes full responsibility for the integrity, accuracy, and originality of the work.

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Introduction

Human beings are social animals biologically predisposed to survival, yet each year, more than 700,000 people die by suicide worldwide.[1] Suicide is defined as death caused by injuring oneself with the intention of dying, while attempted suicide refers to non-fatal acts with similar intent.[2,3] Our current understanding suggests that suicide arises from the intersection of dysregulated emotions, poor social connectivity, and disrupted neurobiology.[4] Risk factors include psychiatric or physical illness, socioeconomic disadvantage, early life trauma (child abuse, child sexual assault), genetics, sex, and access to lethal means.[5] Sex differences also shape patterns, with women being more likely to attempt suicide, whereas men are more likely to die by suicide, often due to the use of more lethal methods.[5]

Understanding how the brain loses life-preserving instincts and rationalises self-destruction remains a central question in the neuroscience community.[6] While the majority of the discourse surrounding suicide has emphasised physiological and social factors, the pathophysiological factors have remained neglected. This review aims to address this gap by integrating evidence to clarify how neurobiological changes contribute to suicidal behaviour. Historically, suicide research has primarily focused on psychological and social frameworks, but recent advancements in neuroimaging, postmortem brain analysis and neurochemical testing have expanded the understanding of the biological changes that correlate to suicidal behaviour.[6,7] These advancements allow us to identify specific changes in brain anatomy and chemistry.[6] Despite this progress, suicide remains a leading cause of death globally, highlighting the need for an improved understanding of the mechanisms by which neurobiological alterations converge to erode survival instincts, leading to fatal outcomes. Emerging evidence has begun to reveal how disruptions in brain circuits, stress-response systems, and neurochemical pathways contribute to the breakdown of survival mechanisms that typically protect against self-harm.[7]

This paper aims to review the pathologic neurobiological mechanisms that erode survival instincts. First, it examines how survival instincts and self-preservation are disrupted by physiological, psychological, and environmental stressors. Second, it explores the neurobiological differences between suicidal and non-suicidal brains, focusing on structural alterations, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, serotonin system abnormalities, and circuit-level dysfunctions. Finally, it highlights areas for future research, including the identification of biomarkers, sex-specific neurobiological differences, and translational strategies to improve prediction and prevention of suicidal behaviour.

Understanding how the brain loses life-preserving instincts and rationalises self-destruction remains a central question in the neuroscience community.

Survival instincts and the mechanisms of self-preservation

Survival instincts are essential for the continuation of a species; they are a complex interplay of physiological responses, psychological processes, and learned behaviours aimed at self-preservation.[8] The process leading to disruption of survival instincts is complex, involving physiological, emotional, biological, genetic and social factors, all of which can influence and exacerbate each other.

Continuous and prolonged emotional strain or trauma can lead to structural and neurochemical alterations in brain anatomy involved in emotional regulation, stress processing and impulse control, including the prefrontal cortex, amygdala and hippocampus.[9-11] Alterations to these areas, together with disrupted serotonergic signalling and altered tryptophan metabolism, can impair mood regulation and stress resilience, increasing vulnerability to suicidal ideation and attempts.[12] Genetic variation affecting serotonergic function, such as polymorphisms in enzymes involved in serotonin synthesis, along with physiological insults such as hypoxia, may further weaken survival instincts and exacerbate this deterioration.[13]

The amygdala works in conjunction with the prefrontal cortex and the hippocampus to identify potential threats, a process central to emotional regulation and self-preservation.[9] The hypothalamus regulates the stress response through the HPA axis, enabling physiological adaptation to danger.[10] The insula plays a role in emotional regulation and interoceptive awareness, allowing recognition of and appropriate response to discomfort and distress.[11] Pain receptors trigger reflexes causing the person to move away from harmful stimuli and alerting them to potential injury, reinforcing injury avoidance.[14] Working in tandem, these structures support self-preservation by facilitating threat detection and avoidance. Dysfunction within these systems has been associated with impaired emotional control and increased vulnerability to self-harm.[15]

While the amygdala, prefrontal circuitry and HPA axis are central to survival and stress regulation, their function is sensitive to prolonged psychological stress and social context. As a result, sociological and psychological theories have been used to explain how sustained emotional distress can override survival mechanisms and contribute to suicidality.

Numerous sociological theories have been posited to explain how suicide continuously occurs across civilisations. Baumeister's escape theory suggests that individuals in overwhelming psychological pain may see suicide as a means of escaping, equating escape with self-preservation – even though the end result is death.[16] Durkheim's sociological theory, among the earliest in the field, shifts the focus from the individual to society, arguing that suicide is often shaped by social integration and regulation.[17] The interpersonal-psychological theory holds that when someone feels burdened and disconnected while acquiring the capacity to overcome the fear of death, the desire for death can become actionable.[18] Despite their differences, these theories all highlight the role of severe emotional distress in eroding survival instincts. Some also partially attribute this breakdown to the uniquely human ability to understand death and plan for the future, which can further erode instincts for self-preservation.[19]

Survival instincts are essential for the continuation of a species; they are a complex interplay of physiological responses, psychological processes, and learned behaviours aimed at self-preservation.

Suicidal brain vs healthy brain: what changes

There are significant neurochemical and anatomical changes in the brains of individuals who die from suicide.[20] Through autopsy and postmortem neuroimaging, researchers have begun to identify specific alterations that set these brains apart from those without a history of suicide, offering insight into the biological underpinnings of suicide risk.[15]

Anatomical differences

Postmortem magnetic resonance imaging (MRI) studies comparing individuals who died by suicide with non-suicide controls demonstrate significantly lower grey matter volume in brain regions responsible for emotional regulation and impulse control, independent of suicide method.[21] These reductions in volume most consistently involve the frontal lobe, a region implicated in behavioural regulation, self-referential processing and decision-making. Reduced grey matter also extends to limbic and paralimbic structures, including the insula and amygdala, as well as cortical regions involved in self-referential processing and social cognition. This indicates structural alterations in neural systems that support emotional awareness and social behaviour.[21]

Structural alterations within these regions have been associated with impaired emotional regulation and reduced impulse control, both of which are associated with increased suicide risk.[20-23] Grey matter reduction has been attributed in part to neuroinflammatory processes commonly reported in major depressive disorders.[24] Supporting this, postmortem studies report increased microglial activation in brain regions governing emotional regulation, reflecting heightened neuroinflammatory activity.[24] Disruption of white matter tracts connecting these regions has also been reported, suggesting that impaired neural communication may further compromise emotional and behavioural regulation.[24] Together, these structural and inflammatory alterations are thought to disrupt communication between interconnected brain regions, providing a neuroanatomical basis for the circuit-level dysfunction observed in suicidality.[19]

Circuit-level dysfunction

In a healthy brain, the orbitofrontal cortex, amygdala and hippocampus form an interconnected prefrontal-limbic circuit that regulates threat identification, emotional response and impulse control.[25,26] The orbitofrontal cortex sends inhibitory signals to the amygdala, reducing feelings of fear, shame, and anger – a process key to self-soothing.[25] The hippocampus supports these processes by providing contextual memories, enabling the amygdala to differentiate between threats and transient stressors, and reinforcing the perception that stress is typically temporary and non-threatening.[26]

Damage to the prefrontal-limbic circuit through neuroinflammation, genetic vulnerability, hypoxia or infection can disrupt communication between the prefrontal cortex and the amygdala, leaving amygdala activity insufficiently regulated and resulting in hyperactivity.[26] Disruption to hippocampal connectivity further compromises threat processing, increasing emotional rigidity and stress sensitivity.[26] These changes may contribute to the intense hopelessness reported by suicidal individuals.[19] As problem-solving capacity becomes impaired, death starts to be perceived as a rational solution.[19] Neuroimaging and clinical studies associate dysfunction within the prefrontal-limbic circuit with increased vulnerability to suicidal behaviour, suggesting that disruption of this circuitry contributes to the loss of survival instincts.[19,26]

There are significant neurochemical and anatomical changes in the brains of individuals who die from suicide.

Hypothalamic-pituitary-adrenal axis

HPA axis dysregulation plays a major role in various

pathophysiological processes associated with suicidal behaviour. The HPA axis plays a crucial role in regulating a person's stress response through modulating specific neurotransmitters. Trauma and prolonged stress are factors that may cause the HPA axis to become dysregulated.[10,27] This dysregulation leads to hypercortisolism, which disrupts immune regulation and increases neuroinflammation through increased cytokine activity.[27] This contributes to the amygdala becoming overreactive, leading to difficulty in controlling negative emotions. If excessive stress continues, the HPA axis can become under-activated, leading to hypercortisolism, which is associated with impulsivity and bluntness. Both extremes of stress dysregulation are harmful, as insufficient stress responsivity may also increase vulnerability to impulsive self-harm.[27]

In postmortem studies, it has been found that suicide victims have elevated corticotropin-releasing hormone in their cerebrospinal fluid.[28] Individuals who have been identified as a suicide risk have been shown to have impaired cortisol suppression when a dexamethasone test is done.[29] One explanation for this dysregulation is that early life trauma and chronic stress lead to epigenetic changes, which affect the feedback system, specifically the methylation of the NR3C1 gene for the glucocorticoid receptors.[30] In many postmortem studies, these receptors are shown to be downregulated in the prefrontal cortex and the hippocampus, parts of the brain vital in controlling the amygdala.[30]

Through autopsy and postmortem neuroimaging, researchers have begun to identify specific alterations that set these brains apart from those without a history of suicide, offering insight into the biological underpinnings of suicide risk.

Serotonergic system dysregulation

Serotonergic system dysregulation is commonly observed in individuals with major depressive disorders and plays a role in suicide pathophysiology.[31-33] In a narrative review of human studies, Sadkowski *et al.* summarised postmortem and cerebrospinal fluid investigations drawn from samples ranging from approximately 50 to over 2,000 participants. The reviewed studies compared individuals who had exhibited suicidal behaviour or died by suicide to non-psychiatric control subjects.[32] Across multiple investigations, central serotonin metabolism was assessed using cerebrospinal fluid concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the primary metabolite of serotonin. These studies consistently reported significantly lower cerebrospinal fluid 5-HIAA levels in suicide victims and individuals experiencing suicidality, indicating reduced central serotonergic turnover.[33] The prefrontal cortex shows an increased number of 5-hydroxytryptamine 2 (5-HT2) receptors, a compensatory response typically seen in 5-HT deficiency states.[34] Genetic variation affecting tryptophan hydroxylase-2 (TPH2), the rate-limiting enzyme for brain serotonin synthesis, may predispose individuals to reduced serotonergic tone, thereby increasing vulnerability to impaired impulse control and suicidality.[13]

The kynurenine pathway is the primary metabolic pathway for tryptophan, an essential amino acid that is crucial in serotonin production.[12] Immune signals, such as interferon-gamma, tumour necrosis factor (TNF)-alpha, and interleukin (IL)-6, activate indoleamine 2,3-dioxygenase (IDO), upregulating this pathway. Elevated levels of these inflammatory markers have been detected in the cerebrospinal fluid of suicide victims.[35] In the presence of these inflammatory markers, the metabolism of tryptophan is upregulated, causing serotonin production to decrease and leading to loss of emotional regulation. Additionally, a by-product of this pathway is quinolinic acid, an N-methyl-D-aspartate (NMDA) agonist that causes oxidative stress in brain regions linked to suicide, including the prefrontal cortex and hippocampus, further amplifying inflammation and neural damage.[12]

Future research in the neurobiology of suicide

Despite substantial progress in understanding the neurobiology of suicide, future research must address the methodological and translational limitations of the existing studies. Most existing literature relies on cross-sectional studies and postmortem analyses. Longitudinal research following high-risk individuals over time is needed to determine whether neurobiological abnormalities precede suicidal ideation or arise as a consequence of chronic stress and major depressive disorders.[6] Such designs would help in distinguishing stable suicide vulnerability markers from transient ones.

Despite substantial progress in understanding the neurobiology of suicide, future research must address the methodological and translational limitations of the existing studies.

Future research should also prioritise the identification of clinically exploitable biomarkers of suicidal risk. Dysregulation of the HPA axis, alterations in the prefrontal-limbic circuit, and neuroinflammatory processes have all been implicated, yet no single marker reliably

predicts suicide risk.[8,23,27] Future studies should focus on identifying biomarkers that may guide the early identification and treatment of suicidality. Advances in computational psychiatry and machine learning may also help to identify complex interactions among variables, thereby improving individualised risk prediction when applied to a sufficiently diverse cohort.[35,36]

Future research should also prioritise the identification of clinically exploitable biomarkers of suicidal risk.

Neuroinflammatory processes in the brain also warrant future research. Evidence suggests that immune activation, cytokine release, and altered tryptophan metabolism via the kynurenine pathway contribute to emotional dysregulation and cognitive rigidity associated with suicidal behaviour.[12,37] However, the contribution of inflammation within the temporal lobe to suicide risk remains poorly defined. Future studies should clarify whether inflammation of the temporal lobe has a substantial risk of downstream consequences of psychological stress, explicitly leading to increased suicide risk. This distinction is essential for evaluating the potential preventive and therapeutic relevance of anti-inflammatory interventions targeting region-specific neuroinflammation.[7,23] Identifying the temporal lobe-specific impact of neuroinflammation is crucial for determining whether inflammatory processes act as antecedent risk mechanisms, acute state markers, or downstream consequences of psychological stress, thereby informing both suicide risk prediction and the timing of targeted anti-inflammatory interventions.[38]

Another area of impact is the sex-specific differences in the neurobiology of suicide. Suicide and self-harm rates, as well as methods, differ markedly between males and females. Much of the neurobiological literature treats these differences as secondary, often analysing males and females together, which may mask important biological distinctions in suicide risk. Hormonal influences and sex-specific stress responses may contribute to suicide risk and warrant further focused investigation.[20,22]

Lastly, ethical innovation remains essential. Suicide research is constrained by stigma, cohort vulnerability, and reliance on retrospective data. Developing methods to study individuals during high-risk periods, within ethically sound frameworks, may be critical to advance prevention strategies.[39]

Conclusion

Suicide risk is influenced by biological, psychological, and social factors. Understanding suicide requires examining how the protective mechanisms of the brain and body fail under these pressures. This is a continuously evolving field, in which the emerging research is unearthing the neurobiological contributions to suicide, creating new opportunities for revolutionary treatments.

Suicide risk is influenced by biological, psychological, and social factors. Understanding suicide requires examining how the protective mechanisms of the brain and body fail under these pressures.

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RCSI smj review

CSF biomarkers: transforming the field of Alzheimer's disease diagnosis

Abstract

Alzheimer's disease is one of the most common neurological disorders, and places a substantial burden on patients and their families. As the field of neurology advances, Alzheimer's disease has evolved from a purely clinical diagnosis to one supported by more specific and accurate prognostic markers, such as cerebrospinal fluid biomarkers. This review explores the pathophysiology of Alzheimer's disease, established and emerging biomarkers, their role in diagnosis, and the challenges and implications associated with their clinical use. Established biomarkers including amyloid beta 42, total tau, and phosphorylated tau, and emerging biomarkers, such as visinin-like protein 1 and synaptosomal-associated protein 25, provide greater insight into the pathophysiology of the disease and enhance diagnostic confidence, especially when measured in tandem. Although biomarkers alone cannot confirm an Alzheimer's diagnosis, when used in conjunction with clinical assessment and neuroimaging, diagnostic precision increases, enabling earlier and more reliable disease detection. Nonetheless, their use raises ethical questions concerning the psychological and social impact of earlier disease detection.

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Declaration of generative AI

During the preparation of this manuscript, the author(s) used generative artificial intelligence (GenAI) to assist, where applicable, with language editing, sentence refinement, and improvement of readability. All content generated or modified using these tools was carefully reviewed and verified by the author, who takes full responsibility for the integrity, accuracy, and originality of the work.

Introduction

Alzheimer's disease (AD) remains the most common cause of dementia worldwide.[1] It is responsible for approximately 60-70% of all dementia cases and affects 55 million people globally.[1] The rising prevalence of AD presents a major global health challenge because of its progressive cognitive and functional decline and its substantial socioeconomic impact. First described in 1906 by Alois Alzheimer, AD was characterised by the presence of amyloid plaques and neurofibrillary tangles in the postmortem autopsy of a patient exhibiting memory loss,

paranoia and behavioural changes.[2] These abnormalities became the defining pathological hallmarks and continue to shape current diagnostic and research approaches. While diagnosis was once strictly limited to a postmortem confirmation, advancements in medical technology have enabled *in vivo* detection through clinical assessment, neuroimaging, and biomarker analysis.[3] Among these is the emerging use of cerebrospinal fluid (CSF) analysis in improving diagnostic accuracy, particularly in early or atypical disease presentation when conventional methods are limited.[4] This review analyses established and novel CSF biomarkers in AD and investigates their use in improving diagnosis.

The pathophysiology of Alzheimer's disease

AD, like many neurological conditions, has multiple theorised mechanisms underlying its pathology. The pathological hallmarks of AD consist of the abnormal accumulation of proteins, including amyloid beta (Aβ) and hyperphosphorylated tau protein, which distinguish it from other neurodegenerative diseases. Aβ accumulation results from the abnormal proteolytic cleavage of the amyloid precursor protein by β-secretase.[5] Inappropriate aggregation of Aβ leads to the formation of insoluble amyloid plaques, which disrupt synaptic communication, causing further neuronal loss, and ultimately contribute to the progression to AD.[5] The accumulation of hyperphosphorylated tau protein occurs due to an imbalance between tau phosphatases and microtubule-associated kinases.[5] Under physiological conditions, phosphorylation of tau protein stabilises microtubular assembly, essential for neuronal development.[5] However, excessive accumulation leads to the production of protein complexes known as neurofibrillary tangles (NFTs), which contribute to neurodegeneration.[5] NFTs are often found in the hippocampal region and the cerebral cortex, significant areas for memory function, and are believed to be the underlying contributors to memory loss associated with AD.[5] Beyond these hallmark proteinopathies, additional mechanisms have been proposed including cerebrovascular disease, neurotransmitter deficits, neuroinflammation, and epigenetics.[5]

Current cerebrospinal fluid biomarkers for Alzheimer's disease

CSF analysis has emerged as an important tool in the diagnosis of AD, with biomarkers such as Aβ42 demonstrating the highest diagnostic accuracy for early detection, followed by total tau (t-tau), and phosphorylated tau (p-tau).[6] Aβ plaques, the pathological hallmark of AD, begin accumulating years before clinical symptoms appear.[7] An inverse relationship exists between Aβ concentrations in CSF and amyloid plaque burden in the brain, demonstrating that CSF levels decrease as amyloid aggregates in neural tissue – a valuable indicator of disease progression.[8] However, the Aβ40/42 ratio provides greater diagnostic reliability, as a reduced ratio more accurately reflects increased cerebral amyloid plaque deposition.[9] Absolute Aβ42 levels can vary due to factors such as CSF dilution and peripheral clearance, limiting their standalone diagnostic utility. Normalising Aβ42 to Aβ40 mitigates these confounding effects. During amyloid plaque formation, Aβ42 declines disproportionately relative to Aβ40, which remains relatively stable, resulting in a marked reduction in the Aβ40/42 ratio. This enhances specificity for AD pathology compared with assessment of individual peptide concentrations, thereby increasing diagnostic confidence, reducing reliance on invasive testing, and improving early detection accuracy.[9]

CSF levels of t-tau reflect the extent of neuronal damage and are elevated in a range of neurodegenerative and acute neurological conditions.[10] Tau is a microtubule-associated protein that stabilises microtubules essential for axonal transport, neuronal integrity, and synaptic function. Under normal conditions, tau is predominantly intracellular and is present at low concentrations in CSF. Neuronal injury results in the release of tau into the CSF, such that higher CSF t-tau levels indicate greater neuronal damage.[11] However, because t-tau lacks disease specificity, it is used in combination with other biomarkers, such as Aβ42, to improve diagnostic precision.[6] In AD, elevated t-tau levels have also been associated with a more rapid rate of clinical progression.[6]

Following the discovery of increased p-tau levels in AD patients, p-tau has emerged as a more specific biomarker capable of distinguishing AD from non-AD neurodegenerative disorders.[12] Under physiological conditions, tau phosphorylation serves as an important marker of synaptic plasticity in the developing brain. In pathological states, hyperphosphorylated tau forms insoluble aggregates that lead to synaptic dysfunction and neuronal cell death. Measurement of p-tau in the CSF shows promise as a biomarker for axonal degeneration and neurofibrillary tangle formation.[12]

Combined biomarker ratios, such as p-tau/Aβ42 and t-tau/Aβ42, enhance diagnostic sensitivity by integrating markers of amyloid deposition with measures of tau-related neurodegeneration, and show strong concordance with neuropathological findings and amyloid positron emission tomography (PET) imaging.[13] These ratios improve diagnostic performance because they reflect the relative burden of AD-specific pathology, rather than relying on absolute biomarker concentrations alone. In clinical practice, it is the degree of abnormality in these biomarker concentrations, rather than their mere presence, that drives diagnostic classification. Incorporation of these

biomarkers into clinical assessment has been shown to alter the diagnosis in approximately 25% of cases, particularly among individuals with mild cognitive impairment (31%) and subjective cognitive decline (29%), thereby improving diagnostic accuracy and informing treatment planning.[13]

Novel cerebrospinal fluid biomarkers for Alzheimer's disease

Beyond the classical tau and amyloid biomarkers, several novel CSF markers have emerged to further refine AD diagnosis. Among these, neurogranin, visinin-like protein 1 (VILIP-1), and synaptosomal-associated protein 25 (SNAP-25) show particular promise in capturing the synaptic and neuronal dysfunction that occurs early in disease progression.[14,15] Neurogranin, a postsynaptic protein involved in synaptic plasticity and memory formation, reflects early synaptic degeneration and neuroinflammatory processes. Elevated levels in CSF have been associated with synaptic loss and cognitive decline, making it a sensitive marker of early neuronal injury.[15] In parallel, SNAP-25, a presynaptic protein essential for neurotransmitter release, has been shown to rise significantly in the CSF of individuals with AD, even during prodromal stages.[15] This further underscores synaptic impairment as a defining feature in early disease stages. Similarly, VILIP-1, which was initially characterised as a marker of acute ischaemic injury, has been found to correlate with neuronal damage in AD and may complement tau-based measures in assessing disease severity.[16] Collectively, these emerging biomarkers enhance the current diagnostic framework by providing insight into the synaptic and neuronal pathophysiology of AD and, when used alongside established markers, may improve diagnostic accuracy, prognostication, and therapeutic monitoring.

Traditional and emerging approaches to diagnosis

The diagnostic evaluation of AD has evolved from a symptom-based approach to a multidimensional framework that integrates clinical assessment, neuroimaging, and biomarker evidence. Traditionally, diagnosis relied on clinical history, cognitive testing, and structural imaging guided by National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) or National Institute on Aging-Alzheimer's Association (NIA-AA) criteria. This diagnostic method demonstrated a sensitivity ranging from 70.9% to 87.3%, and a specificity between 44.3% and 70.8% when compared against neuropathological findings at autopsy.[17] These traditional approaches remain the first diagnostic step, allowing for the exclusion of alternative causes of cognitive decline through neurophysiological studies and imaging in those who exhibit atypical or early-onset presentation – although these techniques often lack the specificity required for a definitive AD diagnosis.

To enhance diagnostic precision, CSF biomarkers have been integrated into the modern diagnostic framework. The results of the biomarkers must always be interpreted with clinical and imaging data, as they are considered as diagnostic adjuncts and cannot be used solely for diagnosis. When integrated into structured diagnostic workflows, CSF biomarkers significantly improve disease classification and contribute to distinguishing AD from frontotemporal, vascular and other non-AD dementias, which tend not to display classic AD biomarkers such as Aβ42 or t-tau.[18]

Despite advances in biomarker development, a comprehensive and detailed clinical evaluation remains the cornerstone of AD diagnosis prior to confirmatory testing. This includes detailed history, physical examination, clinical assessment and laboratory investigations to exclude reversible causes such as vitamin B12 deficiency and thyroid dysfunction.[19] Neuroimaging aids in ruling out structural abnormalities, while cognitive screening tools such as the Mini Mental State Examination and Montreal Cognitive Assessment quantify severity of cognitive impairment.[20] Although these tools are efficient, their diagnostic accuracy may be influenced by education level, language proficiency, and cultural background, showing limited sensitivity in detecting mild cognitive impairment (MCI).[20] CSF biomarker testing is now recommended as a second-line diagnostic tool for complex or uncertain cases, especially when results are expected to influence diagnostic confidence, management decisions or eligibility for disease-modifying therapy.[21] Indications for CSF analysis include: MCI with suspicion of early AD; rapidly progressive cognitive declines; atypical presentations with co-pathology; or, comorbid conditions such as vascular brain injury, TDP-43 encephalopathy, or α-synuclein pathology-related disease.[22]

CSF AD biomarker panels (Aβ42, t-tau, p-tau) provide established *in vivo* evidence of AD pathology and aid in differentiation from non-AD dementias.[18] By bridging traditional clinical assessment and molecular pathophysiology, these biomarkers enable earlier, more confident diagnosis and provide the foundation for patient selection in emerging disease-modifying therapy trials.

Ethical ramifications

The use of CSF biomarkers in Alzheimer's diagnosis, although beneficial, raises many ethical questions regarding patient well-being and the principles of earlier diagnosis of incurable diseases. Disclosing biomarker results respects a patient's autonomy, allowing individuals to understand their health status and plan for the future, especially

regarding advance healthcare directives.[23] However, an early AD diagnosis, or even positive genetic risk factor testing (apolipoprotein E) may provoke adverse psychological reactions.[24] The anticipation of cognitive decline is thought to severely impact mental health, increasing the risk of depression, anxiety, suicidal ideation, and suicide attempts after diagnosis.[25] Beyond psychological effects, an AD diagnosis carries social implications that can negatively impact quality of life and access to care. Due to the nature of the disease progression, patients are often stereotyped as incapable of functioning independently, regardless of their disease stage, and may face discrimination at work or within their households.[26] Additionally, early diagnosis can threaten patients' health insurance eligibility, as companies use existing comorbidities to increase premiums or decrease coverage.[27]

An additional ethical conundrum arises from the limited actionability of an AD diagnosis, stirring a debate on whether physicians should be required to disclose early AD detection. Although earlier diagnosis with CSF biomarkers may be able, to an extent, guide the use of disease-modifying treatments,[27] no treatment can cure or reverse the disease. Furthermore, the effects of emerging therapies are still being studied, and as of now have no conclusive results.[28] An earlier diagnosis cannot predict when patients will decline, the severity of their symptoms, or the impact on their quality of life. Healthcare professionals and patients must therefore consider whether the benefits of an earlier diagnosis outweigh the psychological, social, and practical risks.[27]

Limitations and challenges

Despite these promising advances, several challenges continue to limit the clinical use of CSF biomarkers in AD. Standardisation remains a major issue across laboratories with sample collection, handling, and analytical techniques introducing variability in result reliability.[18] Ongoing international efforts, such as the Global Biomarker Standardization Consortium, aim to co-ordinate protocols and establish universal reference cut-offs to enhance reproducibility and comparability of findings.[29]

Further limitations include the invasive nature of lumbar punctures, increasing patient hesitancy and limiting the possibility of large-scale screening.[18] Additionally, even when samples are obtained, interpretation of CSF biomarkers can be complex. The quantity of biomarkers such as t-tau can vary with age, comorbidities, and acute neurological injuries, potentially leading to diagnostic uncertainty.[30] Although t-tau is valuable when in adjunct with other biomarkers, it still lacks specificity when used in isolation.[31] Results must always be interpreted with the patients' clinical presentations and imaging findings. Furthermore, practical issues of assay cost, access, and lab infrastructure continue to challenge widespread implementation.[30] These limitations highlight the need for a broader, more inclusive biomarker panel that encapsulates the full spectrum of Alzheimer's pathophysiology and can be applied effectively across diverse health settings.

Conclusion

AD remains a major global health challenge; however, the advancements being made in CSF biomarker research have the ability to strongly influence and improve diagnostic accuracy. Established biomarkers such as Aβ42, t-tau, and p-tau have demonstrated strong diagnostic value, while emerging biomarkers such as neurogranin, VILIP-1, and SNAP-25 capture synaptic and neuronal dysfunction that occur early in disease progression. Despite the impact of these investigative developments on improving diagnostic confidence, challenges regarding lack of standardisation, the invasive nature of lumbar puncture, and access disparities still remain. Nevertheless, with improved accuracy, management options for Alzheimer's may be implemented earlier, and may slow disease progression and improve quality of life.

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Listening to the proteome: how molecular wearables could redefine preventive medicine

Abstract

Wearable health technologies have expanded personal access to physiological data, enabling continuous monitoring of heart rate, sleep, glucose levels, and other biometric signals outside clinical settings. Current wearable devices largely measure what happens in the body rather than why it happens, capturing downstream physiological outcomes instead of the molecular processes that precede disease. Emerging organic field-effect transistor (OFET) biosensors offer a pathway toward 'molecular wearables' capable of detecting proteomic signatures such as ubiquitination dynamics, a regulatory signal implicated in cancer, neurodegeneration, immune regulation, and cellular stress. Recent advances in flexible, low-power OFET platforms demonstrate sub-nanomolar sensitivity for protein–protein interaction detection and the potential for integration into skin-interfaced, real-time diagnostic systems. This review examines the ethical and technical limitations of current wearable health technology, the molecular and engineering foundations of OFET-based biosensing, and translational opportunities and challenges in implementing proteomic wearables in preventive medicine. Issues of data validity, psychological impact, accessibility, and health equity are discussed alongside the clinical promise of early molecular detection. OFET-integrated molecular wearables represent a paradigm shift from physiological monitoring to biochemical interpretation, redefining preventive medicine through earlier, more meaningful insights into the molecular origins of disease.

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Introduction

Wearable health technology has transformed how individuals interact with their own physiology. Once confined to hospital monitors, biometric data, heart rate, sleep and glucose levels are now continuously measured through consumer devices wrapped around wrists, clipped to shirts, and embedded in skin patches. These devices promise autonomy and early disease detection, allowing users to take charge of their health outside traditional clinical settings. A news release by the American Heart Association found that 29% of US adults used wearable devices in 2022.[1]

Yet, as devices become more sophisticated, they also expose a profound limitation: they measure what happens to the body, not why it happens. Heart rhythm, temperature, and oxygen saturation are physiological endpoints, surface reflections of deeper biochemical processes. To detect disease earlier and more precisely, future wearables must transition from tracking vital signs to interrogating the molecular mechanisms that underlie them.

At the molecular level, ubiquitination represents one of the most versatile and information-rich biological signals. As an essential post-translational modification regulating protein degradation, stress responses and immune signalling, ubiquitination is increasingly recognised as a key molecular code whose dysregulation contributes to the pathogenesis of cancer,[2] and neurodegenerative[3] and inflammatory disorders.[4] However, monitoring these molecular signatures in real time has been technically unfeasible, until now.

Recent innovations in organic field-effect transistor (OFET)-based biosensors suggest that wearable molecular diagnostics may soon move from imagination to reality.[5] This review explores how such biosensors could bridge the gap between external physiology and internal molecular biology through three key perspectives: first, it outlines the limitations and ethical challenges of existing devices; second, it examines the technical foundations and potential of protein-based sensing platforms; and, finally, it considers how these molecular innovations can be ethically and effectively integrated into clinical and everyday use. Drawing from both the ethical frameworks and the technical promise of OFET-based ubiquitin sensors, it proposes a roadmap for the next era of wearable medicine, one defined not just by measurement, but by meaning.

The current landscape of wearable health technology

Wearable health technology has become a cornerstone of digital health, transforming chronic disease management, fitness tracking, and preventive care. Its growing prevalence, across smartwatches, echocardiogram (ECG) patches, and continuous glucose monitors, has redefined patient autonomy, enabling near-continuous feedback loops between the body and data analytics platforms.[6] Yet, this same flood of physiological data has created new ethical, psychological, and systemic challenges.

Ethical concerns arise from what has been described as a "justice-and-care" framework, which argues that technological progress should be evaluated not only in terms of innovation, but also in relation to fairness and accessibility.[7] The World Health Organization (WHO) echoes this sentiment through its reports on the "digital divide", demonstrating that those most in need of continuous health monitoring, such as older adults and patients with chronic illness, are often least able to access it.[8] High device costs, dependence on internet connectivity, and uneven digital literacy continue to widen global health inequities in the digital era.[8]

Technical reliability is equally critical, as the ethical value of wearable devices is inseparable from their engineering integrity; false positives and data errors can lead not only to clinical inefficiency, but also to psychological harm.[9] The Apple Heart Study, while groundbreaking in scale, reported positive predictive values as low as 34% for atrial fibrillation alerts.[10] When algorithms misfire, technology ceases to empower and begins to erode trust. This reliability gap has measurable human consequences. Researchers at the University of North Carolina found that one in five patients using arrhythmia-monitoring wearables experienced persistent anxiety after false alerts, despite normal cardiac findings.[11] This phenomenon has been described as "hypervigilant self-monitoring", whereby otherwise healthy users internalise device-generated data as evidence of illness.[12] In these cases, wearables designed to reassure instead teach users to live in constant expectation of disease.

Even when technically sound, wearable technologies can overwhelm healthcare systems with unfiltered, patient-generated data. A Synapse Medicine overview states that "alert fatigue happens when health IT systems flood clinicians with so many warnings that they stop paying attention".[13] Without intelligent triage or prioritisation systems, digital health can become clutter rather than clarity.

In short, current wearables excel at monitoring physiology but struggle to interpret biology. They embody a surface-level revolution that has yet to reach the molecular roots of disease. The next generation of devices must sense not only symptoms but their cellular origins, bridging human physiology and molecular pathology. This is precisely where OFET biosensors may transform the field.[14]

The molecular interface: organic field-effect transistor biosensors

At their core, OFETs are flexible, low-power electronic devices capable

of translating molecular interactions into measurable electrical signals. They consist of a semiconducting polymer layer whose conductivity changes in response to biochemical events at its surface. Because OFETs can be fabricated on soft, skin-compatible substrates, they represent a crucial step towards truly molecular wearables, devices that can sense the biochemical 'language' of proteins.

Plastic and organic electronic devices have been shown to be resilient, maintaining electrical performance even when bent, stretched, or immersed in physiological fluid.[15] This durability underscores their suitability for wearable and implantable biosensors and, as demonstrated in organic semiconductor systems such as OFETs, enables integration with biological tissue by mimicking its softness and signal responsiveness.[16] Unlike optical biosensors that rely on optics or fluorescent tags, OFET platforms operate through electrical transduction, making them inherently compatible with miniaturised, flexible circuit architectures.[13,17] They consume minimal power, can be fabricated using scalable roll-to-roll printing methods, and integrate readily with wireless communication modules.[16,18] Together, these properties position OFET-based biosensors as a compelling foundation for skin-interfaced molecular diagnostics.

A recent breakthrough study demonstrated the first OFET-based platform for detecting protein–protein interactions (PPIs) using ubiquitin biology as a model system.[14] The device immobilised an engineered ubiquitin variant, UbV8.2, onto the transistor surface, enabling it to recognise and bind to its partner enzyme, ubiquitin-specific protease 8 (USP8), a deubiquitinase implicated in protein homeostasis and disease.[19] When USP8 bound to UbV8.2, the resulting change in charge distribution across the semiconducting layer produced a quantifiable alteration in current. The sensor achieved sub-nanomolar sensitivity (0.22nM) and exceptional specificity, distinguishing USP8 from unrelated proteins, while requiring no optical labelling or bulky equipment, only the electrical readout of the transistor itself.[14] The work was described as "a novel and robust electrical sensing platform for the detection of PPIs, which is easy to realise and has the potential to be integrated into lab-on-a-chip systems for rapid, point-of-care diagnostics".[14]

Beyond its sensing performance, a major strength of this platform lies in its versatility. The system's versatility arises from its modular design: by swapping the immobilised 'bait' protein, the same platform could theoretically detect a wide range of disease-related targets, including enzymes, viral proteins, cytokines, or antibodies. In general, OFET sensors "use π-conjugated organic semiconductors as electronic materials and are endowed with biological recognition capabilities by proper functionalisation or integration of bio-systems such as DNA strands, antibodies, enzymes and capturing proteins".[17] This inherent adaptability, when combined with further miniaturisation and integration into soft, stretchable substrates, could enable OFET biosensors to monitor biochemical states continuously, paving the way for real-time molecular diagnostics.

A key contribution of this approach lies in its expansion of wearable technologies into the proteomic realm. Traditional devices track macroscopic parameters – heart rate, glucose, temperature – as seen in neonatal and paediatric monitoring systems that continuously record vital signs through skin-interfaced biosensors.[20] In contrast, OFET-based biosensors detect the molecular consequences of disease onset, potentially days or weeks before symptoms arise. For example, dysregulated deubiquitinase activity has been implicated in neurodegenerative disorders such as Parkinson's and Alzheimer's disease, where early detection remains challenging due to the long pre-clinical phase of pathology, the absence of reliable molecular biomarkers, and the tendency for clinical symptoms to appear only after substantial neuronal loss.[21] Embedding a ubiquitin-sensitive OFET patch has the potential to support earlier recognition of molecular disturbances associated with neurodegenerative disease by capturing proteomic changes that emerge before overt clinical decline.[21] Although this application has not yet been demonstrated in humans, its relevance is supported by evidence that disruptions in the ubiquitin–proteasome pathway occur early in disease pathogenesis, positioning molecular wearables as a promising direction for future clinical translation.

Translational implications: from bench to wristband

The consolidation of wearable technology requires a multi-disciplinary approach – a collaboration between clinicians, patients, engineers, and ethicists. OFET-based biosensors can be integrated into wearable technologies because of their high sensitivity to biochemical stimuli, enabling the detection of relevant disease-associated biomarkers in real-time monitoring applications.[22] In oncology, dysregulation of ubiquitination and deubiquitination contributes to tumour progression, as several ubiquitin ligases and deubiquitinases can function as oncogenic drivers or regulators of tumour-suppressor pathways.[23] Altered ubiquitin signalling has likewise been implicated in neurodegenerative disease, where disruptions in proteostasis promote the accumulation of misfolded or aggregated proteins.[21,23] Ubiquitination dynamics also play an important role in host–pathogen interactions, influencing viral replication, immune evasion, and inflammatory responses.[24] When combined with wearable sensing platforms, OFET-based molecular biosensors may therefore provide opportunities for earlier

identification of clinically meaningful molecular disturbances and for monitoring treatment response over time, supporting more timely and targeted therapeutic decision-making.[22]

Furthermore, the integration of OFET-based wearables raises the issue of alerting the patient on constant proteomic feedback. Implementation requires the wearables to provide specific thresholds that correlate with abnormal changes in biomarkers. Low-voltage OFETs operate with minimal power requirements and can be tuned to detect changes in electrical signal corresponding to biomarker fluctuations, allowing threshold levels to be defined for patient and clinician alerts.[25] This would require machine learning as well as prioritising fluctuation of molecular changes over normal benign data.

Ethical considerations are also a priority in implementation of OFET-integrated wearables. Health equity considerations are essential, particularly with respect to affordability, device accessibility, and disparities in digital literacy, as unequal access to digital health technologies can exacerbate existing health inequities.[8] Furthermore, patient autonomy must be addressed, as well as the long-term psychological impact of the wearable technology.[24] Misuse of proteomic information that reveals disease predisposition or variation in drug metabolism may also raise risks of discrimination in insurance or employment, echoing ethical and legal concerns established in the governance of genetic data, such as protections against genetic discrimination in health insurance and employment under the Genetic Information Nondiscrimination Act of 2008 (GINA).[26] Therefore, use of such data must be dealt with carefully. Additionally, OFET-based wearable technology should be affordable for the general public in consideration of health equity. Luckily, OFET biosensors prove to be affordable using low-energy printing methods.[14]

Beyond technical and ethical considerations, the psychological impact of continuous biometric feedback also warrants attention. Continuous exposure to personal health data has been associated with increased stress and anxiety, particularly when individuals feel pressure to maintain 'ideal' readings or interpret minor fluctuations as signs of illness, which may in turn encourage patterns of excessive self-monitoring and self-diagnosis.[12]

In summary, OFET-based wearable health devices seem to have enormous potential for healthcare; however, there are numerous factors to be considered before widespread implementation, particularly the ethical implications of using such devices.

Conclusion

Many current wearable health technologies focus on quantifying physiological outputs such as heart rate, activity levels, and glucose concentration, providing valuable but indirect indicators of health status. In contrast, emerging OFET-based approaches aim to integrate molecular biomarkers into wearable platforms, enabling closer interrogation of the biochemical processes that underlie these physiological signals. Incorporating ubiquitin-based OFET biosensors into wearable devices therefore represents a shift from surface-level physiological monitoring towards molecular-level insight, with the potential to enhance mechanistic understanding of disease processes and support earlier, more targeted clinical intervention.

OFET-based biosensors illustrate the increasing integration of molecular biology with microelectronic systems, bringing together biochemical sensing, device engineering, and clinical application. This convergence raises important ethical considerations, including data governance, equitable access to emerging technologies, and the maintenance of patient trust alongside technical development. In this context, the "justice-and-care" framework emphasises that innovation divorced from accessibility risks reinforcing existing inequities rather than advancing meaningful progress.[7] Because OFET-based biosensors can be fabricated using low-cost, low-power, and scalable printing methods, they may offer a more accessible pathway towards molecular diagnostics, provided that ethical implementation and equitable distribution are addressed in parallel with technological advancement.

Yet, our responsibility extends beyond invention. As the Apple Heart Study and others revealed, even well-meaning data can overwhelm, mislead, or harm.[10] If we are to give patients a molecular mirror, it must reflect truth, not fear. Ethical design demands not just technical precision, but emotional intelligence – technologies that inform without alarming, that empower without isolating.

With further technological and clinical development, molecular wearables may enable the detection of early proteomic changes that arise prior to the onset of clinical symptoms, in some cases potentially weeks or months in advance, thereby supporting earlier intervention and a shift towards more preventive models of care. By providing continuous, biologically relevant data, such systems could facilitate more timely clinical decision-making and improved alignment between molecular biomarkers and therapeutic strategies.

The central challenge is no longer whether wearable technologies can expand health monitoring, but how effectively they can be designed to measure biologically meaningful signals, serve diverse patient populations, and support clinically actionable interpretation. By extending wearable sensing beyond

physiological outputs to molecular biomarkers, molecular wearables have the potential to enhance insight into disease mechanisms and enable more precise, data-driven approaches to prevention, diagnosis, and treatment.

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RCSI smj review

Incisions of the past, visions of the future: mapping the evolution of minimally invasive surgery

Abstract

Minimally invasive surgery (MIS) has transformed surgical practice over the past four decades, shifting operative innovation from larger incisions to precision-based, tissue-sparing access. From the first laparoscopic cholecystectomy in 1987 to the widespread adoption of robotic-assisted platforms, MIS has consistently demonstrated benefits including reduced postoperative pain, shorter hospital stays, and faster return to function, while maintaining equivalent clinical outcomes to open surgery. The evolution of MIS represents not only technological advancement, but a fundamental change in surgical philosophy, prioritising reduced physiological disruption and improved ergonomics. Emerging modalities such as single-port laparoscopy and natural orifice transluminal endoscopic surgery (NOTES) extend towards scarless intervention, supported by advances in flexible endoscopy and robotic integration. However, challenges persist in cost, training demands, global accessibility, and equitable implementation, particularly in resource-limited settings. Looking ahead, digital innovation, including artificial intelligence and tele-surgical capability, is poised to augment intraoperative decision-making, standardise training, and expand access to specialist expertise. This review maps the historical trajectory, comparative outcomes, and philosophical shifts underpinning MIS while examining the opportunities and ethical considerations shaping its future. Ultimately, the next era of surgery will be defined not only by minimal invasiveness, but by the integration of precision, equity, and global collaboration.

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Introduction: a history of minimally invasive surgery

Over the past four decades, minimally invasive surgery (MIS) has transformed modern surgical practice, replacing large incisions with precise, image-guided approaches that promote faster recovery, reduced pain, and shorter hospital stays. What began as an experimental concept in the 1980s has now become the cornerstone of many surgical disciplines. The first laparoscopic cholecystectomy, performed in 1987, marked the beginning of this revolution, demonstrating that smaller incisions could achieve comparable clinical outcomes to open procedures.[1] By the early 1990s, advancements in endoscopic imaging and electrocautery devices allowed surgeons to refine these techniques and apply them to an expanding range of operations.[2,3]

Laparoscopy not only improved patient outcomes but also reshaped global access to safe surgery. Studies have consistently shown that laparoscopic procedures result in decreased postoperative complications, improved cosmesis, and earlier return to normal function when compared with open surgery.[4,5] These benefits, coupled with continual technological progress, paved the way for the next major development in the field: robotic-assisted surgery (RAS). Introduced in the early 2000s, robotic platforms enhanced surgical dexterity and precision through articulated instruments, tremor filtration, and high-definition three-dimensional imaging.[6] Although initially limited by cost and size, newer modular systems such as the Versius and Hugo RAS platforms have expanded accessibility while integrating advanced features like haptic feedback and artificial intelligence (AI) for better image recognition and workflow optimisation.[7,8]

Today, MIS continues to evolve towards even less invasive approaches. Innovations such as single-port laparoscopy and natural orifice transluminal endoscopic surgery (NOTES) aim to further minimise tissue trauma and eliminate visible scarring.[9,10] These emerging techniques, together with advances in flexible endoscopy and robotic integration, represent the next chapter in the evolution of surgical access. This review will trace that progression, from the early days of laparoscopy to the frontier of scarless surgery, while exploring the evidence, limitations, and implications for future clinical practice.

The evolution of minimally invasive surgery: a shift in surgical philosophy

Rather than a simple progression of technologies, the evolution of MIS reflects a fundamental shift in how surgeons conceptualise surgical access and patient recovery. Early laparoscopy demonstrated that surgical success did not depend on the size of an incision, but on the ability to manipulate tissues effectively with minimal physiological disruption. This change in philosophy, prioritising reduced trauma and faster recovery, has since shaped every subsequent innovation in MIS.[11]

Three major factors have driven this transformation. The first is the pursuit of enhanced visualisation, beginning with fibre-optic imaging and advancing to high-definition digital platforms that enable finer anatomical discrimination.[2] The second is the continuous improvement in instrument dexterity, with surgeons moving from rigid laparoscopic tools to articulating, wristed, and eventually robotic instruments capable of mimicking or surpassing natural hand movements.[6] Last is the growing demand for procedural ergonomics and sustainability: recognising that surgeon fatigue and comfort directly influence patient safety and outcomes.[12]

Over the past four decades, minimally invasive surgery (MIS) has transformed modern surgical practice, replacing large incisions with precise, image-guided approaches that promote faster recovery, reduced pain, and shorter hospital stays.

RAS emerged not as a replacement for laparoscopy but as a response to these evolving priorities. By addressing limitations such as restricted movement and muscle strain, robotic systems expanded what could be achieved through minimal access rather than redefining the field. Similarly, innovations in single-port surgery and flexible endoscopy reflect a broader movement towards reducing parietal trauma while maintaining or improving operative control.[9]

Taken together, the "evolution" of MIS is best understood not as a chronological sequence but as a progressive refinement in how surgeons balance invasiveness, precision, and patient-centred outcomes.[11] Each innovation, whether robotic, single port, or endoscopic, represents a different solution to the same challenge: how to intervene effectively while disturbing the body as little as possible.[13] This shift in mindset set the stage for the most radical reimagining of access to date – NOTES – where the surgical incision is no longer a point of limitation but a variable to be eliminated entirely.[10]

The rise of scarless access: NOTES and single-port innovations

As the field of MIS continues to evolve, attention has turned towards the next frontier of surgical access, achieving comparable outcomes without leaving visible scars. This concept, known as NOTES, involves

accessing the peritoneal cavity through natural orifices such as the mouth, vagina, stomach, or rectum, eliminating the need for abdominal incisions.[10] Initially conceptualised in animal studies, NOTES emerged as a logical extension of endoscopic and laparoscopic principles.[14] The first successful human transgastric peritoneoscopy was reported in 2004, and subsequent years have seen steady exploration of transvaginal and transoral approaches for a variety of procedures.[15-17]

In transvaginal NOTES (vNOTES), the posterior vaginal fornix provides access to the peritoneal cavity, allowing operations such as cholecystectomy, appendectomy, adnexal surgery, and hysterectomy to be performed with excellent cosmetic and postoperative results.[18,19] Comparative studies and systematic reviews suggest that vNOTES hysterectomy achieves equivalent or improved outcomes relative to laparoscopic or vaginal techniques, particularly in terms of pain, blood loss, and hospital stay.[20] Similarly, transoral endoscopic thyroidectomy vestibular approach (TOETVA), a derivative of NOTES, has been widely adopted in Asia and increasingly in Western centres.[21] TOETVA enables removal of thyroid and parathyroid tissue via small incisions hidden within the oral vestibule, resulting in no visible neck scar.[22] Reports indicate low complication rates and high patient satisfaction when performed by experienced surgeons.[23]

Taken together, the "evolution" of MIS is best understood not as a chronological sequence but as a progressive refinement in how surgeons balance invasiveness, precision, and patient-centred outcomes.

Other natural orifice approaches, including transgastric and transrectal routes, remain largely investigational due to concerns about infection, instrument triangulation, and reliable closure of internal entry points.[10] Nevertheless, ongoing refinements in flexible endoscopy, insufflation control, and endoscopic suturing continue to expand feasibility and safety profiles. Meanwhile, hybrid procedures that combine NOTES with single-port or conventional laparoscopy, such as "vNOTES-assisted" colectomy or cholecystectomy, are being trialled to balance innovation with operative stability.[24]

Single-port surgery, while conceptually distinct, shares the same goal of reducing parietal trauma and improving cosmesis. By introducing all instruments through a single umbilical incision, single-port laparoscopy leaves a virtually invisible scar and simplifies wound care.[25] Meta-analyses comparing single-port and multi-port laparoscopy report comparable complication rates, with modest reductions in early postoperative pain and subsequently higher patient satisfaction.[26] The technique's primary limitation lies in ergonomic strain and reduced instrument manipulation; however, the implementation of curved and articulating tools has substantially mitigated these challenges.[12] Robotic integration further enhances precision, offering "tremor filtration" and improved spatial control within the confined single-port field.[27]

The progression from traditional laparoscopy to NOTES and single-port innovations underscores a consistent surgical theme: the pursuit of less invasive yet equally effective access. While widespread adoption of these techniques remains limited by training demands and costs, ongoing technological refinement continues to bring the once theoretical idea of truly scarless surgery closer to clinical reality.

Comparative outcomes and challenges: the benchmark standard

Laparoscopy remains the foundation upon which all subsequent minimally invasive modalities are built. Its reproducibility, safety profile, and established evidence base have made it the global benchmark for MIS.[11] Meta-analyses and multicentre randomised trials consistently demonstrate reductions in postoperative pain, wound infection, and length of stay compared with open surgery.[28] For procedures such as appendectomy, colectomy, and fundoplication, laparoscopy achieves equivalent oncologic and functional outcomes with improved patient satisfaction.[29]

Laparoscopy remains the foundation upon which all subsequent minimally invasive modalities are built.

However, important limitations persist, not only at the technical level, but within the evidence base supporting MIS adoption. In addition to challenges related to surgeon ergonomics, and restricted instrument articulation, outcomes in MIS are strongly influenced by surgeon-specific factors.[30] Learning curves and individual operative style vary considerably between surgeons, making performance difficult to standardise and complicating interpretation of comparative studies.[31] Cost also remains a major barrier to implementation; beyond acquisition, robotic systems require ongoing expenditure for disposable instruments, maintenance contracts, and training infrastructure, limiting availability in resource-constrained settings and widening global disparities in access.[32] Although MIS techniques are generally safe, documented complications and unresolved uncertainties remain, including longer operative times during early adoption, device-related malfunctions, and concerns around access site closure in NOTES and single-port procedures.[33]

Taken together, these limitations highlight that the evolution of MIS reflects not only technological progress, but also variability in human performance, resource accessibility, and the maturity of the supporting evidence.

Beyond technical and clinical outcomes, the evolution of MIS also raises important ethical considerations. High-cost laparoscopic and robotic platforms risk widening inequities in access, particularly where limited resources challenge equitable distribution of surgical technology.[33,34] The steep learning curve associated with many MIS techniques further introduces ethical questions regarding trainee supervision, transparency during early adoption, and patient safety.[34,35] Additionally, the introduction of experimental MIS approaches requires strengthened informed consent processes to ensure that patients understand associated uncertainties and potential risks.[36] As MIS becomes increasingly integrated with digital and AI-enabled platforms, concerns surrounding data governance, privacy, and accountability come to the forefront.[37] Addressing these ethical dimensions is essential to ensure that MIS evolves in a manner that is not only technologically innovative, but also socially responsible and patient centred.

Robotic-assisted surgery: precision at a price

RAS was introduced to address the ergonomic and technical constraints of laparoscopy.[38,39] The da Vinci system, the most widely adopted platform, offers enhanced dexterity through modified instruments and a three-dimensional magnified view.[40] Clinical studies across oncological and gynaecological surgery have demonstrated lower conversion rates and improved dissection precision compared with conventional laparoscopy.[41-43] In robotic prostatectomy, for instance, patients experience reduced blood loss and shorter hospitalisation, although functional outcomes such as continence and potency remain comparable.[44]

RAS was introduced to address the ergonomic and technical constraints of laparoscopy.

The principal challenge of RAS lies in its cost. The high expense of equipment, maintenance, and disposable instruments limits its widespread adoption, particularly in resource-constrained settings.[45] Additionally, despite improvements in surgeon comfort, evidence suggests that operative times are typically longer than those for laparoscopy during the early learning curve.[46] Nevertheless, as newer platforms like Versius and Hugo RAS enter the market, increased competition may reduce costs and expand accessibility.

Single-port surgery: minimal access, maximum constraint

Single-port laparoscopy emerged as a natural evolution of the multiport approach, motivated by the desire to further minimise scarring and parietal trauma. Randomised controlled trials indicate comparable safety and complication rates to conventional laparoscopy, with modest reductions in postoperative pain and improved cosmetic satisfaction.[9] However, ergonomic challenges like instrument collision and limited triangulation remain major barriers.[47] Furthermore, single-port approaches have been associated with longer operative times and greater procedural complexity during early surgeon experience, which may contribute to higher open surgery conversion rates and variability in outcomes.[9] There is also evidence of increased port-site hernia risk following single-port access compared with conventional laparoscopy, representing a distinct complication that warrants clinical consideration.[48] These challenges, together with a steeper learning curve and the need for specialised techniques, further constrain broad implementation of single-port surgery despite its cosmetic advantages.[49]

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Recent advancements in flexible and articulating instruments have improved efficiency, while robotic single-port systems (such as the da Vinci SP platform) offer enhanced precision and access in confined spaces.[50] Early studies in urology and general surgery show promising outcomes, particularly for transabdominal prostatectomy, although widespread adoption remains limited by cost and training requirements.[51]

Training, accessibility, and equity in innovation

Beyond clinical outcomes, the adoption of MIS technologies raises important questions of equity and global accessibility. Robotic and NOTES platforms require high capital investment and specialised infrastructure, making their implementation particularly challenging in low- and middle-income countries (LMICs).[52] However, the barriers extend beyond acquisition costs. Even when advanced surgical equipment is available in LMIC settings, limited access to routine maintenance, consumables and reliable technical support frequently undermines their sustained use and functionality, which can compromise programme sustainability and deter investment in advanced surgical modalities.[53-55] Workforce

capacity also remains a key limitation; shortages of trained surgeons, anaesthetists, and biomedical engineers, combined with limited exposure to MIS during residency, constrain independent practice and contribute to dependence on visiting surgical missions or short-term training initiatives.[54]

Beyond clinical outcomes, the adoption of MIS technologies raises important questions of equity and global accessibility.

These systemic limitations risk deepening global disparities in surgical care, where populations already face limited access to safe, affordable surgery. In this context, MIS adoption may preferentially benefit urban tertiary centres while bypassing rural or underserved regions, widening intranational inequities. Training initiatives and simulation-based education have demonstrated value in reducing learning curves and strengthening local capacity; however, their long-term impact depends on parallel investment in infrastructure, supply chains, and workforce retention.[56] Ultimately, the success of next-generation MIS technologies will not only depend on innovation, but on models of dissemination that prioritise affordability, capacity building, and equitable access across diverse health system settings.[56]

Conclusion

From the first laparoscopic cholecystectomy to the new age of robotic and natural orifice surgery, the innovations in MIS reflect the pursuit of precision with minimal trauma. Each generation of innovation has advanced this mission by refining access, enhancing visualisation, and reducing physiological disruption. Yet, as surgical tools become more sophisticated, the challenges surrounding cost, training, and equitable access grow equally complex.

Looking forward, the next transformation in MIS will likely be driven by digital integration. AI, augmented reality, and machine learning are poised to redefine intraoperative navigation. AI-assisted video analysis already enables automated identification of critical structures, real-time error recognition, and skill assessment, all of which could improve safety and standardise training.[41] Similarly, augmented reality platforms are being trialled to overlay anatomical landmarks during laparoscopic and robotic procedures, improving spatial awareness and reducing cognitive load.[57]

From the first laparoscopic cholecystectomy to the new age of robotic and natural orifice surgery, the innovations in MIS reflect the pursuit of precision with minimal trauma.

Another frontier is tele-surgery. Initially demonstrated in 2001 during Operation Lindbergh, it has re-emerged as a realistic tool thanks to high-speed networks and low-latency robotic control.[58] With increasing accessibility to modular and portable robotic systems, remote-assisted operations could one day bridge the gap between specialised surgical centres and under-resourced hospitals, offering real-time mentorship and access to expertise.

Ethical and practical challenges, however, remain. Ensuring equitable access to these technologies across socioeconomic and geographic lines is critical to prevent widening global disparities in surgical care. Moreover, with automation and AI-assisted decision-making entering the operative field, questions of accountability and surgical autonomy are becoming increasingly relevant.[59] Integrating ethics, policy, and data governance into surgical education will therefore be as essential as mastering new techniques.

Ultimately, the future of MIS lies not only beyond the incision, but at the intersection of human expertise and global collaboration. If innovation is guided by equity and education, the next era of surgery will not just be minimally invasive, but maximally inclusive.

Ultimately, the future of MIS lies not only beyond the incision, but at the intersection of human expertise and global collaboration.

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RCSI smj review

A review of convolutional neural network image classification and segmentation in brain tumour MRI

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Declaration of generative AI
During the preparation of this manuscript, the author(s) used generative artificial intelligence (GenAI) to assist, where applicable, with language editing, sentence refinement, and improvement of readability. All content generated or modified using these tools was carefully reviewed and verified by the author, who takes full responsibility for the integrity, accuracy, and originality of the work.

Abstract

Brain tumours present substantial diagnostic and therapeutic challenges; even small tumours can disrupt neurological function, while aggressive variants such as glioblastomas progress rapidly despite multimodal care. Magnetic resonance imaging (MRI) is central to the evaluation of brain tumours due to its superior soft tissue contrast and multimodal, multiplanar capability. Convolutional neural networks (CNNs) now achieve high in-domain performance for MRI-based classification and produce voxel-wise segmentations that support biopsy targeting, resection planning, and radiotherapy. This review synthesises recent work on CNN classification and segmentation pipelines, emphasising preprocessing, transfer learning, and hybrid systems that pair calibrated probabilities with anatomically coherent masks. It also highlights current limitations that impede clinical integration, such as small or unbalanced cohorts, limited reporting of failure modes, and limited generalisability. Finally, priorities for the field are discussed, such as: standardised datasets and splits; adequate preprocessing; and, modelling advances that exploit volumetric context, multi-modal inputs, and semi-supervised learning. With these practices, promising preliminary results can mature into reliable, multi-institution decision support.

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Table 1: Brief descriptions of some of the most common types of brain tumour.[1-2,42-45]

Type of tumour	Description
Astrocytoma	Astrocytomas arise from astrocytes. Low-grade astrocytomas are typically benign, whereas high-grade astrocytomas are malignant and highly aggressive.[2]
Glioblastoma	Glioblastomas are the most aggressive type of astrocytoma, known for their rapid growth and poor prognosis despite aggressive treatment efforts.[42]
Medulloblastoma	Medulloblastomas are malignant brain tumours originating in the cerebellum. Cells spread through cerebrospinal fluid, requiring immediate treatment.[43]
Meningioma	Meningiomas arise from the meninges. They are generally benign, with a small percentage being malignant.[44]
Oligodendroglioma	Oligodendrogliomas arise from oligodendrocytes, which are the cells that produce the myelin sheath. These tumours are either benign and low grade or malignant and high grade.[45]
Schwannoma	Schwannomas arise from Schwann cells. They are typically benign but can lead to acoustic neuromas.[1]

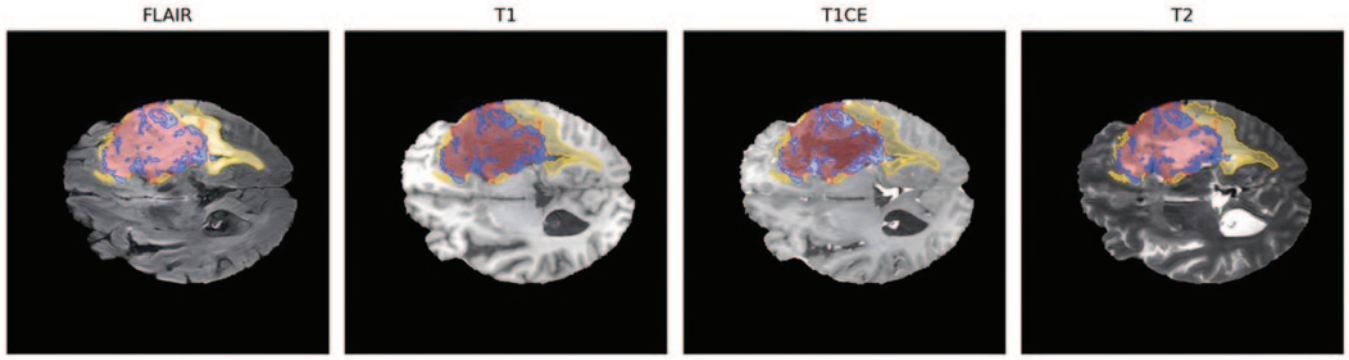

FIGURE 1: MRI of a patient with a glioblastoma imaged in four modalities: FLAIR; T1; T1 contrast-enhanced (T1CE); and, T2. Red represents the tumour core, blue represents enhancing tumour regions, and yellow represents the surrounding oedema. Image reproduced from the BraTS 2020 dataset under CC BY 4.0.[12,13,46,47]

Introduction

Brain tumours are masses arising from cancerous cells found in the brain. Even small tumours have been shown to significantly impair function.[1-3] Magnetic resonance imaging (MRI) is the primary tool for diagnostic evaluation due to its unique ability to image soft tissues with high resolution.[4,5] Convolutional neural networks (CNN) offer automated extraction of image features for classification and segmentation. In brain tumour MRI, artificial intelligence (AI) models show promise for diagnostic applications.[6-9] This review synthesises recent literature on CNN-based classification and segmentation for brain tumour MRI. It aims to summarise performance and workflows, examine how preprocessing and architectural choices influence generalisation, and highlight where hybrid systems improve clinical eligibility.[10,11] Finally, the paper will discuss reporting practices and research directions needed to convert strong in-sample results into reliable, multi-institution decision support.

Brain tumours

Brain tumours are either primary (arising from cells within the central nervous system) or secondary (metastatic), which can then be malignant or benign.[1] Malignant tumours disseminate and often require multimodal intervention, whereas benign masses are generally less invasive.[1-3] Prognosis varies by type, grade, location, and patient status.[2] **Table 1** summarises common tumour characteristics and clinical behaviour.

MRI is the gold standard for brain tumour diagnosis due to its superior soft tissue contrast. Various contrasts can be used to visualise different aspects: T1 depicts anatomy; T1 contrast enhancement highlights the blood–brain barrier; T2 emphasises oedema; and, fluid-attenuated inversion recovery (FLAIR) suppresses cerebrospinal fluid (CSF).[4,5] **Figure 1** illustrates these modalities to display subregions of a glioblastoma.[12,13]

Deep learning and neural networks

AI models rely on labelled databases drawn from public sources such as RIDER, Harvard Dataverse, Figshare, and Kaggle.[14-19] A typical CNN workflow (**Figure 2A**) has three steps: (1) import datasets; (2) pre-process via intensity normalisation, augmentation, and cropping; and, (3) model inference and training.[20-24] Model training, as illustrated in **Figure 2B**, shows convolutional layers forming feature maps while pooling downsamples to ensure robustness.[25] This is

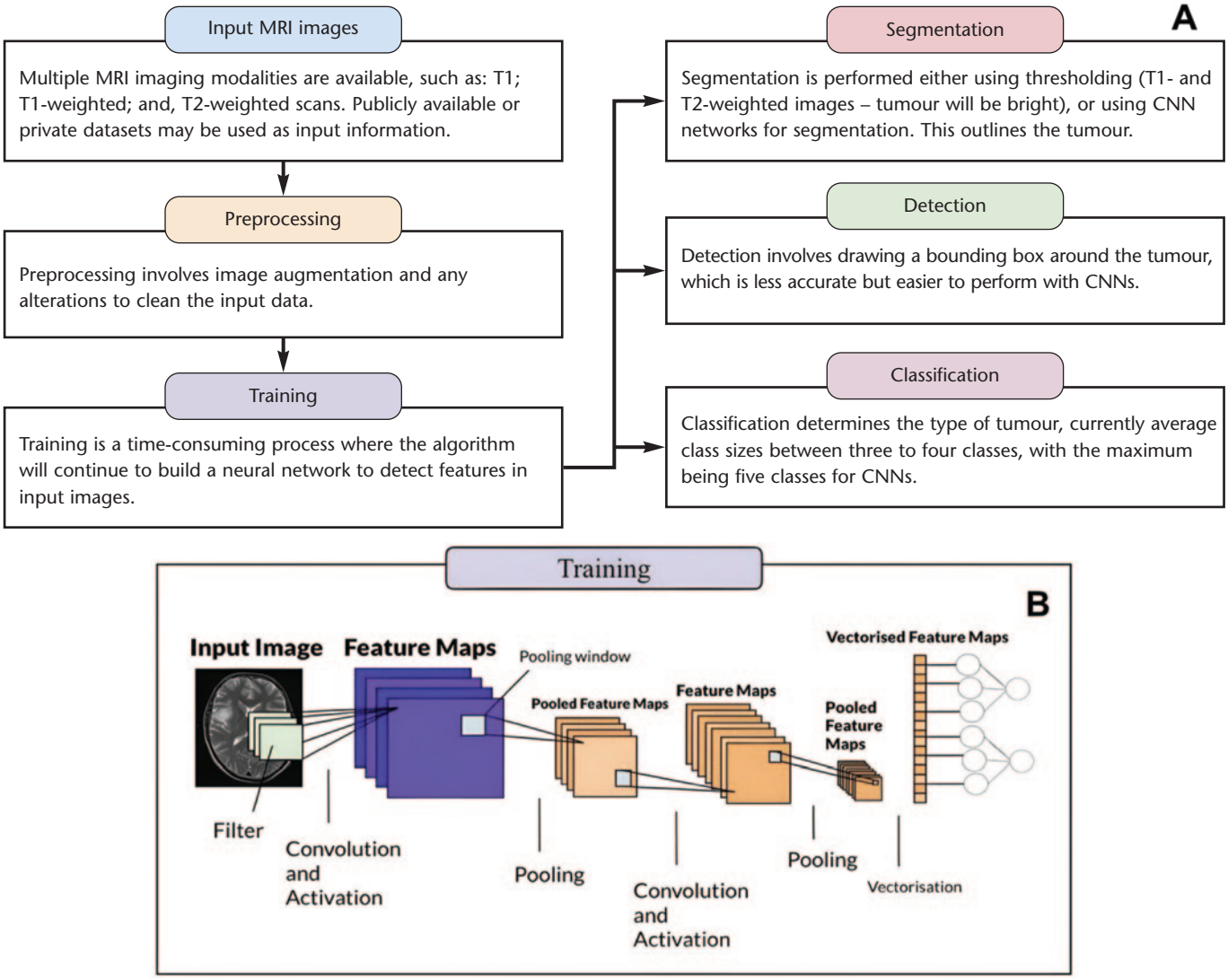

FIGURE 2: A) Diagram illustrating the full workflow for training a CNN model: inputting images, preprocessing, training, and the possible model outputs. B) Illustration by Younis et al. *displays the inner workings of a classification CNN processing a brain MRI image during the training stage. Reproduced from Younis* et al. *Appl Sci. 2022;12:7282. CC BY 4.0 – no changes.*[20-25]

repeated until features are fully connected to vector feature maps. Then, a softmax function produces calibrated class probabilities for classification tasks.[26]

A common practice for developing neural networks is transfer learning, where pre-trained models serve as backbones.[27] **Table 2** summarises commonly used model backbones.

Related works on published models

PubMed, IEEE Xplore, and arXiv (January 2017 to November 2025) were surveyed for peer-reviewed studies on MRI brain tumour classification, detection, or segmentation using neural networks. Papers selected reported quantitative performance on human MRI with sufficient methodological detail, prioritising studies with patient-level splits and external test sets. All model classification categories are: glioma; meningioma; pituitary gland tumour; and, normal scan. **Tables 3** and **4** provide a summary of papers published on the identified classification and segmentation models.

Four-class clinical baselines and architecture efficiency

Across common four-class datasets (glioma, meningioma, pituitary, normal), many single-site studies report high in-domain accuracy, often >97-99%. Abdelaziz Ismael *et al.* (2020) report a straightforward ResNet-50 transfer-learning pipeline, without bespoke architectural tuning, achieving 99% accuracy, while Banerjee *et al.* (2017) reached 97% accuracy with a task-specific CNN.[8,28] On top of accuracy, several papers present high-performance lightweight models, such as Vimala *et al.* (2023), delivering 99.1% accuracy with an EfficientNet-B2 model using streamlined pipelines, which is promising for high-throughput

Table 2: Common pre-trained CNN model architectures.[24,48-52]

Model	Description
AlexNet	AlexNet uses rectified linear unit (ReLU) activation functions, dropout layers to mitigate overfitting, and data augmentation techniques that reduce error rates.[24]
VGGNet	VGGNet uses small 3x3 convolution filters to capture fine details and patterns in images.[48]
Inception	Inception concatenates feature maps of different sizes, which capture visual information at different scales, significantly improving accuracy and reducing computational cost.[49]
EfficientNet	EfficientNet uses compound scaling of depth, width, and resolution to create the B0-B7 family, producing compoundingly complex models.[50]
ResNet	ResNet uses residual learning, which learns the difference between the input and desired output.[51]
DenseNet	DenseNet connects every layer to each other in a feed-forward fashion. This leads to increased connection density but higher performance.[52]

Table 3: Summary of papers developing brain tumour classification models.[6,8,28-35,38-40]

Reference	Algorithm	Accuracy	Findings	Drawbacks
Ismael *et al.* (2020)[8]	ResNet-50	99%	Highest accuracy on respective database	No architecture changes or optimisation
Banerjee *et al.* (2017)[28]	Custom	97%	High accuracy on custom CNN network	No comparison to other models or databases
Díaz-Pernas *et al.* (2021)[6]	Custom	97%	High accuracy on custom CNN network	Unbalanced dataset leads to model bias. No cross-database validation
Kurup *et al.* (2020)[35]	CapsNet	87-93%	Preprocessing shifts validation accuracy by 6%	Did not compare the effects of preprocessing on other models
Zhou *et al.* (2019)[32]	DenseNet	71-92%	The model achieved high accuracy on a public dataset	Cross-database accuracy was low, implying low generalisability
Mathivanan *et al.* (2024)[30]	ResNet152 VGG19 DenseNet169 MobileNetV3	97%	ResNet152/MobileNetV3 proved effective for brain tumour classification	No cross-database validation
Patil and Kirange (2023)[33]	VGG16	98%	VGG16 achieved high accuracy on specified dataset	Small and unbalanced database. No cross-database validation
Raj *et al.* (2020)[38]	BrainNet	98%	Model presented high accuracy	Insufficient methodological detail
Sarhan (2020)[39]	Custom	99%	High accuracy on a custom CNN network	No comparison to other models
Sultan *et al.* (2019)[31]	AlexNet InceptionV3 VGGNets	98%	Fine-tuned VGG16 had the highest accuracy compared to listed model	Single imaging modality. Limited dataset size
Ucuzal *et al.* (2019)[40]	CapsNet	97%	Highest accuracy from CapsNet	Minimal model comparisons. Absence of key reportable statistics
Vimala *et al.* (2023)[29]	EfficientNetB0-B4	99%	High accuracy given small model backbone	Small and unbalanced dataset
Anaraki *et al.* (2019)[34]	Custom	94%	Custom CNN model with adequate model comparisons and validation	Lower accuracy than state-of-the-art models

environments.[29] Mathivanan *et al.* (2024) demonstrate that both heavyweight backbones, such as ResNet-152, and lightweight backbones, such as MobileNetV3, can achieve similar classification accuracy.[30] Shifting to segmentation models, Díaz-Pernas *et al.* (2021) achieved high classification accuracy while also segmenting the classified tumours, providing masks that support surgical planning and radiation targeting.[6] Sultan *et al.* (2019) display a high accuracy fine-tuned VGG16, with significant preprocessing complexity.[31]

Table 4: Summary of papers developing brain tumour segmentation and detection models.[7,9,10,36,37,41]

Reference	Algorithm	Accuracy	Findings	Drawbacks
Chen *et al.* (2019)[9]	Custom	84%	Training incorporates label distribution and softmax loss functions	No post-processing integration. Multiple training phases
Myronenko (2018)[36]	Custom	82%	Novel 3D encoder-decoder with variation auto-encoder (VAE) regularisation	No cross-database validation
Kamnitsas *et al.* (2017)[7]	Custom	84%	Significant improvements in BRaTS 2015 and ISLES 2015 benchmarks	Training is not end to end, leading to manual CRF configuration
Özyurt *et al.* (2020)[41]	Custom	98%	Custom CNN without transfer learning achieved high accuracy	No comparisons made with other models. No cross-database validation
Sharif *et al.* (2021)[10]	InceptionV3 YOLOv2	97%	Model testing on multiple BRaTS datasets shows generalisability	Increased computational load and time were also caused by lack of feature fusion
Zhao *et al.* (2018)[37]	FCNN/CRF	84%	Improved tumour subregion segmentation with appearance of spatial consistency	2D FCNNs, cannot utilise volumetric data
Amin *et al.* (2019)[11]	Fusion of AlexNet/ GoogleLeNet	99%	Cross-database analysis implies generalisability with high accuracy	Fusion was marginally better than each model individually

Magnetic resonance imaging (MRI) is the primary tool for diagnostic evaluation due to its unique ability to image soft tissues with high resolution. Convolutional neural networks (CNN) offer automated extraction of image features for classification and segmentation.

Data quality, external validity, and generalisation

For patient care, external validity matters more than single-dataset perfection. Zhou *et al.* (2019) displayed an accuracy of 92% on a public dataset, which sank to 71% on a private cohort, arguing that cross-database testing on unseen data should be mandatory before clinical claims.[32] High headline accuracies often rest on small or unbalanced cohorts, such as Patil and Kirange (2023) and Vimala *et al.* (2023), which both lack external tests, inviting optimistic estimates and possible minority-class errors.[29,33] Other papers show a promising shift towards cross-database analysis, such as Amin *et al.* (2019), which includes cross-database evaluation while still reporting accuracies of 99%.[11] Anaraki *et al.* (2019) reported validation accuracy of 94%, shifting the emphasis from a single top-line number to methodology and reproducibility.[34] Sharif *et al.* (2021) evaluated a custom CNN model across multiple BraTS datasets, yielding an averaged 97% accuracy, but providing an honest read of performance under heterogeneous curation rather than a single split – arguably more important than a single high-accuracy statistic.[10]

Preprocessing and augmentation for clinically rigorous models

Preprocessing and augmentation are clinically relevant methods to stabilise performance across environments. Kurup *et al.* (2020) reported 6% swings in validation accuracy from preprocessing alone, supporting the need for intensity normalisation and preprocessing augmentations to reduce case- and site-specific variance.[35] Conversely, optimiser/architecture explorations without robust pipelines can post high accuracy but not be clinically generalisable. For example, Myronenko (2018) reported high accuracy for a segmentation model, yet left the model's generalisability to clinical data uncertain without external tests.[36] Mathivanan *et al.* (2024) demonstrated that MobileNetV3 rivals heavyweight models; however, they lacked ample cross-database analysis.[30] Meanwhile, Zhao's (2018) multi-Brain Tumor Image Segmentation Benchmark (BraTS) evaluation with preprocessing illustrates that broader curation typically lowers accuracy but yields a truer picture of robustness.[37]

Segmentation and hybrids: deployment readiness

Segmentation papers contribute clinically relevant advances in delineating tumour, non-enhancing core, and oedema features that guide biopsy targeting, resection margins, and radiotherapy.

Kamnitsas *et al.* (2017) and Chen *et al.* (2019) improve multimodal BRaTS/ischaemic stroke lesion segmentation (ISLES) delineation, showing that boundary-aware post-processing can refine outputs.[7,9] However, they also note some practical limits, such as how 2D CNNs under-utilise volumetric context, and conditional random field tuning can be fragile in boundary delineation. Hybrid systems, such as those described by Díaz-Pernas *et al.* (2021), that combine classification with segmentation, move towards calibrated probabilities and anatomically coherent masks that can be reconciled with endocrine work-ups for surgical corridors and longitudinal response assessment.[6] On readiness for real-time or near-scanner use, there are encouraging studies, such as Vimala *et al.* (2023), showing EfficientNet-B2 at 99% with lean preprocessing, good for latency, although external generalisation remains to be proven due to a lack of cross-database validation.[29] Methodologically, Raj *et al.* (2020) and Sarhan (2020) have strong baselines; however, they do not display training/latency details.[38,39] Similarly, Ucuzal *et al.* (2019) and Özyurt *et al.* (2020) lack confusion matrices or cross-database comparisons, limiting crucial statistics that clinicians need for clinical integration.[40,41] Three clinically important points are worth highlighting. First, calibration: most papers do not report reliability curves or calibrated probabilities, yet clinical models need well-calibrated outputs, not just high accuracy, to set safe decision thresholds. Second, explainability: simple heatmaps can be unstable; clearer, anatomy-aware explanations, such as segmentation masks shown in Díaz-Pernas *et al.*, are preferable (2021).[6] Lastly, boundary-refined outputs are easier for radiologists and surgeons to use to design treatment plans.

Future works and conclusion

Today's CNNs are near deployment ready for basic clinical support, such as triage or initial four-class differential, provided they are embedded in clinical workflows and validated beyond single-site/single-database test splits. Strong baselines show that various backbones can be used according to local computing and staffing needs with comparable accuracy.[8,28,29] The path to broader deployment is clear, making external validity paramount and adopting standardised, metadata-rich public splits with routine cross-database reporting. Zhou *et al.*'s cross-database drop in accuracy is a cautionary signal (2019), whereas other models show that cross-database evaluation is feasible.[10,11,32] Preprocessing and augmentation are necessary safety controls, as they increase generalisability and can significantly improve model accuracy.[35] Clinically legible outputs with boundary-aware and anatomically coherent masks are essential for longitudinal response assessment.[6,7] Such improvements will enable expansion into richer classification taxonomies, semi-supervised regimes, and volumetric/3D spatiotemporal models, turning today's impressive in-domain metrics into dependable, multi-institution decision support.

Today's CNNs are near deployment ready for basic clinical support, such as triage or initial four-class differential, provided they are embedded in clinical workflows and validated beyond single-site/single-database test splits.

Glossary of terms
Augmentation: Artificial modification of existing training data to increase diversity and improve generalisation.
Bespoke architectural tuning: Task-specific customisation of a model architecture.
Boundary-aware: Model or method focusing specifically on object edges or borders.
Coherent segmentation masks: Segmentation outputs that are spatially consistent and anatomically plausible.
Confusion matrices: A specific type of figure showing the relationship between true labels and predicted labels.
Convolution: A mathematical operation in which a small filter scans an image to extract patterns.
Downsampling: Reducing the spatial resolution of an image to analyse large-scale patterns as training progresses.
Heavyweight backbones: Large, computationally demanding model backbones.
Heterogeneous curation: The construction of a dataset from multiple different data sources for the same task.
Hybrid systems: Systems that combine different model types, methods, or data sources.
Intensity normalisation: A preprocessing step adjusting image intensity to a consistent range.
Lightweight backbones: Smaller, more efficient model backbones.
Metadata-rich public split: Publicly available dataset splits including detailed information about each case.
Minority-class errors: Prediction mistakes affecting underrepresented classes in a dataset.
Pipeline: The full sequence of workflow steps, from data loading, preprocessing, and model training, to evaluation.
Pooling: A type of downsampling that reduces the size of feature maps while retaining the important information.

Glossary of terms (continued)
Post-processing: Operations applied after model prediction to refine the output.
Preprocessing: Operations applied to raw data before model training begins to improve quality.
Robustness: The ability of a model to maintain reliable performance over noise, variability, or imperfect input data.
Segmentation: The process of an AI model outlining a region of interest within an image.
Segmentation masks: Pixel-wise or voxel-wise label maps denoting the regions of interest in an image.
Single split: Data is only collected from one training group, leading to a lack of diversity.
Softmax: A function that converts raw model outputs into class probabilities that sum to 100%.
Transfer learning: A method in which a model uses knowledge learned from a previous task/dataset on new data.
Vector feature maps: Numerical representations of data produced by a network, stored as arrays.
Vectorisation: Representing data or features in vector form, such as images broken into pixel intensities.
Volumetric context: The 3D information from adjacent slices, helping the model to understand structure continuity.
Voxel: A unit of measurement in volumetric imaging of 1x1x1 pixels.
Voxel-wise: Assigning a class label to each individual voxel in a 3D image.

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Branches of the Human Spirit by Kanishka Bhalotia

This ink-on-paper piece, created in the Gond art style, represents the evolution of medicine as an organic unfolding over time. We see this motif through the depiction of human evolution. A central theme is growth, illustrated by the humanoid figure transforming into a mango tree, symbolising the natural progression of civilisation and innovation. The human heart mirrors the branches of the tree, conveying that we are not just in our environment but intrinsically connected to it. The maximalist aesthetic draws inspiration from traditional Indian Gond art, a folk style that reminds us of a deeper connection to nature. Overall, medical knowledge has grown over time like a tree and will continue to develop if we nurture the field, progressively expanding our vast library of knowledge.

The gendered experience of psychosis, substance use and incarceration: a call for trauma-informed care

RCSI medical student SAMANTHA BLOOM highlights the need for gender- and trauma-informed interventions in the treatment of women with psychosis and substance use disorders.

Psychosis and substance use disorders in women often stem from intersecting experiences of gender-based violence, childhood trauma, and systemic neglect. Despite this, mental health systems remain largely gender neutral, inadvertently failing to address these realities. Understanding gendered pathways shaping women's mental health, particularly those rooted in early victimisation, is therefore critical to providing effective care.

Through the experience of Patient X, this perspective underscores

the need for gender- and trauma-informed interventions, and calls for a shift away from punitive approaches towards models that promote meaningful recovery and justice.

Psychosis and substance use disorders in women often stem from intersecting experiences of gender-based violence, childhood trauma, and systemic neglect.

The human context

Patient X was admitted under the Mental Health Act 2001 after presenting to the emergency department with persecutory delusions on a background of polysubstance use. She believed that her partner had been poisoning her, and that she could not trust him or anyone around her, including her mother and son. She questioned her partner, who "did not deny" that he was poisoning her. Despite this, she felt that she would be alone without him.

Patient X lived with only her partner, who controlled her finances. A large amount of their money went towards crack cocaine. Her partner was her dealer, her financial advisor, her landlord, and her only friend. She had two children living in foster care, and had been arrested repeatedly for disorderly conduct during psychotic episodes. She was trapped in a cycle of control, trauma, and substance use – one that cannot be broken easily, even with adequate medical treatment.

Her story is not unique; it echoes the "gendered pathways" model described by Salisbury *et al.*[1] This model demonstrates how childhood victimisation, low social capital, and relational control converge to sustain cycles of substance use and incarceration.

Understanding gendered pathways shaping women's mental health, particularly those rooted in early victimisation, is therefore critical to providing effective care.

Pathway to substance use

In the gendered pathways model,[1] three major pathways were found to be related to substance use and incarceration:

1. Pathway A – childhood victimisation: abuse early in life contributes to mental illness and substance use later on.
2. Pathway B – relational control: dysfunctional intimate relationships reduce self-efficacy, leading, and learned helplessness, and entrap women in dependent relationships.
3. Pathway C – social disadvantage: low levels of human capital, such as education and family support, lead to increased vulnerability to crime and marginalisation.

Patient X's life mirrors each of these pathways. As a child, her father abandoned their family, and her mother frequently had adult men in their home. She reported experiencing physical and sexual abuse at their hands throughout her childhood. She left school at 16, resulting in the loss of educational opportunity and structural support. She became involved in a volatile relationship, leading to her first incarceration for domestic violence. Little education and a criminal record resulted in few employment options, and substance use began to take over her life. She later developed substance-induced psychosis, and has been arrested and incarcerated on multiple occasions for disorderly conduct during episodes of psychosis. Her previous partner died of an overdose, leaving her as a young single mother, vulnerable to dependence in future relationships, such as her current one.

Through the experience of Patient X, this perspective underscores the need for gender- and trauma-informed interventions, and calls for a shift away from punitive approaches towards models that promote meaningful recovery and justice.

Identifiable and reproducible pathways leading to mental illness, substance use, and incarceration of women exist, yet women still fall victim to these pathways.[2] Most clinical and correctional responses remain reactive, such as incarceration, rather than preventive.

The way forward

Relationships and self-efficacy

These pathways beg for a unique and pointed solution. A meta-analysis in 2016 by Gobeil *et al.*[3] demonstrated that women who were incarcerated and had experienced gendered issues responded better to interventions targeted at women, rather than non-gendered interventions. Pathways A, B, and C can be used as a framework to identify areas for interventions.

Andrews *et al.*[4] studied mothers who use substances and their engagement with intervention services. The Break the Cycle service in Canada uses a woman-centred focus, and includes things like

childcare and promoting mother–child relationships in its services.[4] Treatment for substance use often takes an individualised approach, which has been shown to be effective in males.[5] However, a relational approach with programmes specific to parenting components has been shown to be more effective in women.[6]

This is demonstrated by Patient X, who has two children in foster care, and has limited contact with them. She described wanting to have greater contact with her children, and said that her role as "mother" brings her hope. Being a mother was one of her only social goals, one that could help to increase her self-efficacy and self-esteem. Studies have found this phenomenon to be true for multiple women, where the mother–child relationship acts as a protective factor and a positive influence for change.[7]

Relationship-based programmes that include mother–child services may be able to increase self-efficacy and social capital through peer bonding in group therapy, supportive relationships with staff, and family bonding. Andrews *et al.*[4] also argue that the effectiveness of the Break the Cycle programme includes long-term service provision. They do not use predetermined amounts of time for their programming, meaning that women can engage with the service over years.[4] This is part of their relational philosophy, which understands that women may have mistrust of services, and need time to develop comfort in engaging with them.[4]

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Early interventions

Early interventions can also be used to target each pathway. The Break the Cycle programme offers a prenatal intervention, where at-risk women can begin engaging with services during a pivotal life stage – one that has previously been identified as a target area for change in women.[4] Women who engaged prenatally were more likely to continue using Break the Cycle services, and had more long-term engagement.[4] In addition to the therapeutic benefits offered by the services, early engagement may indirectly reduce childhood victimisation, while increasing self-efficacy with regard to motherhood.

Targeting Pathway A involves intervention from the time of pregnancy to early adulthood. Childhood victimisation is a complex issue that can be recognised across a variety of settings, including by a paediatrician, at school, and at home. The term "toxic trio" has been used to describe risk factors for child abuse, and includes: domestic violence; parental mental health/learning issues; and, parental alcohol and drug use.[8] A more extensive and thorough risk assessment is warranted, as the toxic trio may be too narrow in scope or too difficult to identify.[8]

The Break the Cycle programme offers a prenatal intervention, where at-risk women can begin engaging with services during a pivotal life stage – one that has previously been identified as a target area for change in women.

A 2023 meta-analysis by Ferragut *et al.*[9] explored the effectiveness of childhood sexual abuse prevention programmes on knowledge acquisition. The prevention programmes mostly took place in schools, and taught children about inappropriate relationships and how to seek help.[9] The study found that participating in the programmes increased knowledge about abuse and children's ability to protect themselves.[9] A robust, systemic approach to preventing childhood victimisation is essential to protecting children's health and reducing long-term consequences such as mental illness, substance use, and incarceration.

Other early intervention programmes target girls during adolescence to prevent school dropout, or facilitate a return to school. Quantum Opportunity, a programme that uses long-term case follow-up to engage with students over years, has successfully decreased dropout rates.[10] Programmes like this, which emphasise long-term relationships, can be particularly effective for women and girls who benefit from relational interventions.

Other early intervention programmes target girls during adolescence to prevent school dropout, or facilitate a return to school.

Challenges in treatment

Improving the health outcomes of individuals like Patient X is possible, but there are challenges that need to be addressed. These challenges exist at the level of the individual, the family, and the community.

At the level of the individual, engagement with services can pose an issue.[4] There may exist a lack of readiness for change, a mistrust of

services, or other factors that prevent an individual from connecting with services.[4] This underscores the importance of early intervention and a population-based approach, such as ensuring that every child who exhibits risk factors, such as absenteeism, has the opportunity to engage with programmes like Quantum Opportunity. At the familial level, limited social support, as well as difficult or abusive relationships, can hinder service use and make change more difficult.[1]

Improving the health outcomes of individuals like Patient X is possible, but there are challenges that need to be addressed.

The community and wider society continues to rely on incarceration for women with mental health and substance abuse problems. Although more alternative services and treatment options are being offered, forensic records still serve to further victimise women and continue to trap them in a cycle.[1]

Conclusion

Patient X's life has been coloured by challenges and trauma. Her life trajectory was changed at a young age by sexual abuse, ultimately contributing to her polysubstance use, incarceration, and mental health problems. It is imperative to move beyond a symptom management approach, and recognise the gendered pathways affecting women. Gender-informed care, including relational frameworks and long-term therapeutic relationships, can more effectively support women and help to break cycles that have persisted for far too long.

Gender-informed care, including relational frameworks and long-term therapeutic relationships, can more effectively support women and help to break cycles that have persisted for far too long.

Disclosure

This article is based on a composite of multiple patient encounters. No single patient is represented and identifying details have been altered to preserve anonymity.

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The garden we carry

RCSI medical student RIDA SHAHBAZ shares the lessons she learned from her time visiting palliative care patients.

I asked a 97-year-old dementia patient what the secret to happiness was. She stared back at me and blinked twice, the corners of her mouth slightly upturned.

"You see, everybody had their own gardens", she began. "And that garden – you learned how to look after it. Where to keep certain vegetables. We had everything. No fridges. Nobody could do it now, but we had no refrigerator, no icebox – now look at it."

Too much.

"We have too much. People are not as happy; they're greedier – they've got lots, but they want more. They're not happy with what they got. We were happy with the little we had from the garden. They don't do that now; they just go to the store."

School. "We had to walk to school in the morning and evening. In the winter, a farmer had two horses and a sleigh, so if it snowed really deeply, he would pick up the children along the way and take us to school: two horses and a big sleigh. We had no furniture that wasn't needed. It was interesting – I wouldn't take back anything."

I continued to ask, "Is there something you regret?"

"No, I don't think so. There are things that maybe I did … but I don't know. There was so much to do. The kids wouldn't do it nowadays, but we used to do it. It was our job. You know, when you stop to think about it, we were so *happy*. In our winters, I got stuck in a snow bank once, and Mama had to get me. My mum was down [in] the house, looking out the window, and she was laughing at me. She came to the door – I can still see it. She's laughing, and here I am crying, 'Mum, help me'. It was beautiful. I was brought up in a wonderful time. You girls have nothing in comparison. And we had no toys – Dad would make us things. I was born after the First World War, during the Depression. Everyone had nothing. Everyone had their own garden. What you didn't have, you would share. We would appreciate half a spoon of sugar. Everybody was the *same* – we didn't have much. You know, it was the best part of our lives. We made it with nothing, and I am so thankful I went through that hard time."

She pointed at my blouse – "I never had anything like that."

"I understand it. What we went through, you will never understand. My mum used to cry because she didn't have any sugar. Some days, I would go up the hill and ask for half a cup of sugar. No one does that now. Everybody was happy. If you were sick, all the women would go back to your place tomorrow to clean your floor and change your bed; we did that. You wouldn't see that kind of thing now. *Never.* Sometimes I'll sit down and go through a few things. I can't get over how people have changed so much. We had *nothing*. I went through the Great Depression. I *understand* it. I'm not jealous of anyone. I went to school barefoot – no shoes."

"I am a *simple, plain old girl*. I don't need expensive things. We were so happy. God came into this world with nothing. And I may be going with anything."

I spent my summer visiting palliative care patients, and that is when my perspective of medicine shifted. During my time volunteering at the long-term care home, I would visit patients two to three times a week, and spend time talking or reading to them. There was a 97-year-old woman in particular, with whom I spent most of my time. We would end up talking for hours, not aware of time slipping by – as if catching up with an old friend. She had been diagnosed with dementia, yet there was something extraordinary about our interactions. Every week, when I came in to see her, she was beyond joyful to have a visitor, yet she couldn't recall who I was or that I had come in just a few days before. During our long conversations, she would tell me about her family, her childhood living through the Great Depression, and the joys and sorrows of her long life. She was the best storyteller I had ever met, and she recalled these details as if they were carefully sewn into her memories – no neurological disease could take that away from her. I became a familiar stranger to her, someone she greeted with joy, even though dementia erased me each week. She explained how much it meant to her that I was coming in to see her, aware that she might not remember me tomorrow. I will never forget what she told me the last time I saw her: "I wish they would come more. People don't realise it, but visitors are needed in these places. Not necessarily family, but simply just visitors. It means so much, and you meet some wonderful people". Listening to her stories week after week, I began to understand that medicine is made of moments like this: quiet, ordinary, deeply human.

She was the best storyteller I had ever met, and she recalled these details as if they were carefully sewn into her memories – no neurological disease could take that away from her.

What it means to care

This is the moment I understood that medicine is so much more than a consultation, a prescription, a diagnosis. It's about *understanding*. It's about cultivating a relationship with your patient that is separate from their condition or illness. Many of the palliative care patients I visited didn't have family visiting them frequently, and several expressed the loneliness they felt watching the world pass them by through TV screens or newspapers. I realised that there was so much to learn from end-of-life care. What I have observed in the healthcare field is that many professionals fail to develop a level of understanding with their patients. They don't *see* them. And for many palliative care patients, that's all the treatment they need: to be seen.

Spending time with her changed my understanding of what it means to care for a patient. Before that summer, I thought medicine was something you *did* – something active, measurable, and clinical. I used to think healing meant improving numbers, adjusting medications, or finding the proper diagnosis. But week after week, she showed me another kind of medicine, the kind that doesn't fit cleanly into charts or guidelines. She taught me that care can be quiet. It can be found in listening to the same story told three times in one afternoon with the same enthusiasm. It can be found in showing up, even when the person you are showing up for doesn't remember your name. And it can be found in recognising that a patient's world is not limited to their medical history – it's shaped by their memories, their fears, their loneliness, and their longing to have a purpose.

Before that summer, I thought medicine was something you did – something active, measurable, and clinical.

As a student doctor, this experience reshaped how I think about my future role. It made me far more aware of the emotional weight patients carry into the clinic or hospital room – a weight that often goes unnoticed because it cannot be measured. I learned how easy it is to overlook the human being behind the symptoms, especially in fast-paced environments. Her stories, full of joy and hardship, reminded me that every patient's life stretches far beyond the moment I meet them. They have entire histories – whole gardens – built long before illness entered the picture. Understanding this has made me more intentional with how I communicate, how I sit down beside someone, and how I listen. It taught me that the small, seemingly insignificant interactions often matter the most.

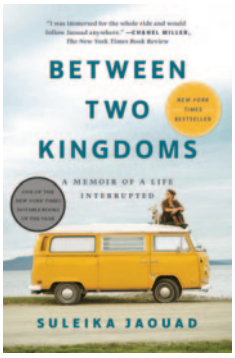
It also profoundly changed the way I view the patient experience. Many of the residents I met were not longing for another blood test, or another scan, or even another treatment. What they missed was connection. They wanted to be remembered, to be visited, to feel like their stories still had a place in the world. Her words, "visitors are needed in these places" echo in my mind often. Patients do not stop needing to be seen once their disease becomes incurable. If anything, the need becomes greater. That summer taught me that dignity, presence, and companionship are forms of medicine too – ones that can soften a person's final chapter in a way no prescription ever could.

Disclosure

Written informed consent for publication was obtained from the patient's next of kin, and potentially identifiable details have been obscured to preserve anonymity.

What *Between Two Kingdoms* reveals about illness and survival

Between Two Kingdoms examines illness as a prolonged condition of uncertainty rather than a narrative of recovery, says Senior Student Staff Writer SAGAR KOTHARI.



Between Two Kingdoms: A Memoir of a Life Interrupted
Publisher: Random House Publishing Group
Published: 2021
ISBN: 9780399588594

Suleika Jaouad's *Between Two Kingdoms: A Memoir of a Life Interrupted* traces a young woman's experience of serious illness and its aftermath, but avoids the conventional arc of diagnosis, struggle, and resolution. Instead, the memoir emphasises uncertainty. It begins not with leukaemia, but with symptoms that are diffuse and easily dismissed: fatigue, recurrent infections, and a growing sense that the body is unreliable. These early chapters are among the book's strongest, capturing how illness often develops gradually and without clear explanation.

Jaouad describes seeking medical care and receiving reassurance while continuing to meet expectations placed on her. Rather than dramatising error or neglect, the narrative shows how both patient and healthcare system accommodate uncertainty, particularly when the patient appears young and functional. Over time, unexplained symptoms lead to self-doubt and the normalisation of discomfort. The reader comes to understand chronic illness not as a single disruptive event, but as a process in which uncertainty becomes routine.

Inside the Kingdom of the Sick

When Jaouad is diagnosed with acute myeloid leukaemia, the memoir shifts into the structured environment of hospitalisation and treatment, a space she calls the "Kingdom of the Sick". Even here, the writing remains restrained. Chemotherapy, transplant, and isolation are described through repetition and routine, rather than dramatic turning points. Time is organised by lab results and medication schedules, privacy is limited, and the body becomes subject to constant evaluation.

These sections focus less on physical suffering than on the narrowing of identity under treatment. Jaouad remains aware of her pre-morbid self, but the demands of care leave little space for that identity to persist. Moments of effective care are those that recognise this tension: a clinician who listens carefully, a nurse who responds to discomfort, or a provider who avoids premature reassurance. Such interactions are small, but they shape how illness is experienced and remembered.

The limits of recovery

The memoir's second half turns to life after treatment, addressing a stage of illness that is often overlooked. Remission does not restore clarity or ease. Instead, Jaouad struggles with expectations that survival should bring closure or gratitude. In response, she travels across the United States, meeting people whose lives have been shaped by illness, grief, or long-term change. These encounters expand the memoir's scope, situating her experience within a broader landscape of survivorship.

Here, *Between Two Kingdoms* makes a central claim: recovery does not mean returning to a previous version of oneself. Survival requires adjustment, and meaning is developed through ongoing effort rather than resolution. Jaouad does not impose a clear conclusion on this process, allowing uncertainty to remain.

Style and meaning

As a memoir, the book is marked by control and precision. Jaouad relies on careful observation and accumulation rather than overt commentary, allowing experience to speak for itself. Illness is not framed as inspirational or heroic, nor is it reduced to endurance. Instead, it is shown to affect relationships, goals, and self-understanding in ways that continue well beyond treatment.

For readers preparing to work with patients facing cancer or chronic illness, *Between Two Kingdoms* offers sustained insight into the patient's perspective, from early symptoms through to long-term survival. It is a reminder that medicine unfolds not only in decisive moments, but in long stretches of uncertainty, and that attention to those spaces matters more than is often acknowledged.

RCSIsmj abstract

Pulmonary hypertension in Oman: multimodal evaluation of invasive haemodynamics

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Background

Pulmonary hypertension (PH) diagnosis requires invasive and resource-intensive confirmation by right-heart catheterisation (RHC).[1] Routinely collected non-invasive metrics may help to identify patients at high risk of pulmonary vascular disease; however, regional data that integrate multimodal non-invasive assessment with invasive haemodynamics remain scarce in the Middle East.[2,3] This study characterises an Omani cohort undergoing RHC for suspected PH and evaluates the ability of routine non-invasive markers to identify severe pulmonary vascular disease.

Methods

We retrospectively analysed adults undergoing RHC for suspected PH at the National Heart Center, Royal Hospital (Muscat, Oman) from January 2020 to July 2025. The analysis included patients with pulmonary arterial hypertension (PAH; Group 1) and chronic thromboembolic pulmonary hypertension (CTEPH; Group 4). This study was approved by the Research & Ethics Commitee of the Royal Hospital, Muscat, Oman (RH/2025/214). We evaluated routinely collected non-invasive markers, including echocardiographic right ventricular systolic pressure (RVSP) and tricuspid annular plane systolic excursion (TAPSE), six-minute walk distance (6MWD), N-terminal pro B-type natriuretic peptide (NT-proBNP), and the pulmonary artery-to-aorta ratio (PA:A) from computed tomography, for correlation with invasively derived pulmonary vascular resistance (PVR). A multivariable logistic regression model was developed to predict severe PVR, defined as a PVR ≥5 Wood units (WU).[4]

Results

Seventy-two patients were included (PAH 58; CTEPH 14); median age 44.5 years, 68% female. Pre-capillary PH accounted for 95.8%. Median mean pulmonary artery pressure (mPAP) was 47mmHg (interquartile range [IQR] 38-58), pulmonary capillary wedge pressure (PCWP) was 10.2mmHg (IQR 7.4-13.6), and cardiac output was 4.5L/min (IQR 3.8-5.4). Median RVSP was 72mmHg (IQR 55-95), and median TAPSE was 16.9mm (IQR 13.2-20.4). Compared with PAH, CTEPH patients had higher RVSP (84 vs 66mmHg; p=0.005) and lower TAPSE (12.4 vs 17.0mm; p=0.002). The composite non-invasive model showed moderate discrimination for predicting PVR ≥5WU (area under the curve [AUC] 0.66±0.07).

Conclusions

Non-invasive markers demonstrated moderate discrimination for identifying severe pulmonary vascular disease (PVR ≥5WU), supporting their role in early triage and prioritisation for RHC, while RHC remains essential for definitive diagnosis and phenotyping. In Oman, where PH care and invasive testing are typically centralised, multimodal non-invasive assessment may help clinicians to identify higher-risk patients earlier, expedite referral to specialist services, and improve pathway efficiency.

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RCSI smj abstract

Comparative *in vitro* antioxidant and cytotoxic activities of *Garcinia mangostana* and *Coriandrum sativum* extracts in A549 lung cancer cells

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Declaration of generative AI
During the preparation of this manuscript, the author(s) used generative artificial intelligence (GenAI) to assist, where applicable, with language editing, sentence refinement, and improvement of readability. All content generated or modified using these tools was carefully reviewed and verified by the author, who takes full responsibility for the integrity, accuracy, and originality of the work.

Objectives

Lung cancer is the leading cause of cancer-related death worldwide.[1] Although several chemotherapeutic agents are currently available, their effectiveness is often limited by the development of resistance,[2] highlighting the need for novel therapeutic approaches. Mangosteen (*Garcinia mangostana*), a fruit native to Southeast Asia, and coriander (*Coriandrum sativum*), a widely used culinary herb, have attracted increasing scientific interest due to their reported antioxidant and anticancer effects.[3,4] These effects are attributed to their high concentration of phenolic compounds, which scavenge free radicals by neutralising reactive oxygen species and nitrogen species.[5] This study investigates the potential antioxidant and cytotoxic activity of mangosteen and coriander against pulmonary cancer cells.

Methods

Mangosteen and coriander extracts were prepared using 90% ethanol. Antioxidant capacity was assessed using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2 -azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays. Cytotoxicity against human pulmonary cancer cells (A549) was evaluated using the 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. Extract concentration ranges were determined based on preliminary experiments. Antioxidant assays were performed using concentrations of 0-8mg/mL, while cytotoxicity assays used concentrations of 5-80µg/mL. Vehicle-treated cells containing 0.2% dimethyl sulfoxide (DMSO) served as the negative control, and doxorubicin was used as the positive control. Combination extracts were prepared at a fixed 1:1 ratio. Experiments were performed in triplicate and repeated across at least three independent experiments. Data were analysed using one-way analysis of variance (ANOVA), followed by Tukey's post-hoc test, with $p<0.05$ considered statistically significant. Data are presented as mean +/- standard deviation.

Results

Mangosteen extract demonstrated greater antioxidant activity than coriander, with lower half-maximal inhibitory concentration (IC50) values in both the DPPH assay (21.4±2.1µg/mL vs 68.2±1.9µg/mL) and the ABTS assay (16.9±1.5µg/mL vs 44.5±2.3µg/mL). Mangosteen extract also demonstrated higher cytotoxic potency against A549 cells (IC50=18.7±1.6µg/mL), whereas coriander showed lower activity than mangosteen (IC50=72.3±4.9µg/mL). The combination extract of mangosteen and coriander yielded intermediate potency (IC50=29.6±2.2µg/mL). All reported comparisons were statistically significant ($p<0.05$).

Conclusion

Both mangosteen and coriander exhibited antioxidant and cytotoxic activity against lung cancer cells, with mangosteen demonstrating superior potency. These findings support further investigation into their molecular mechanisms and potential interactions between their bioactive components.

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