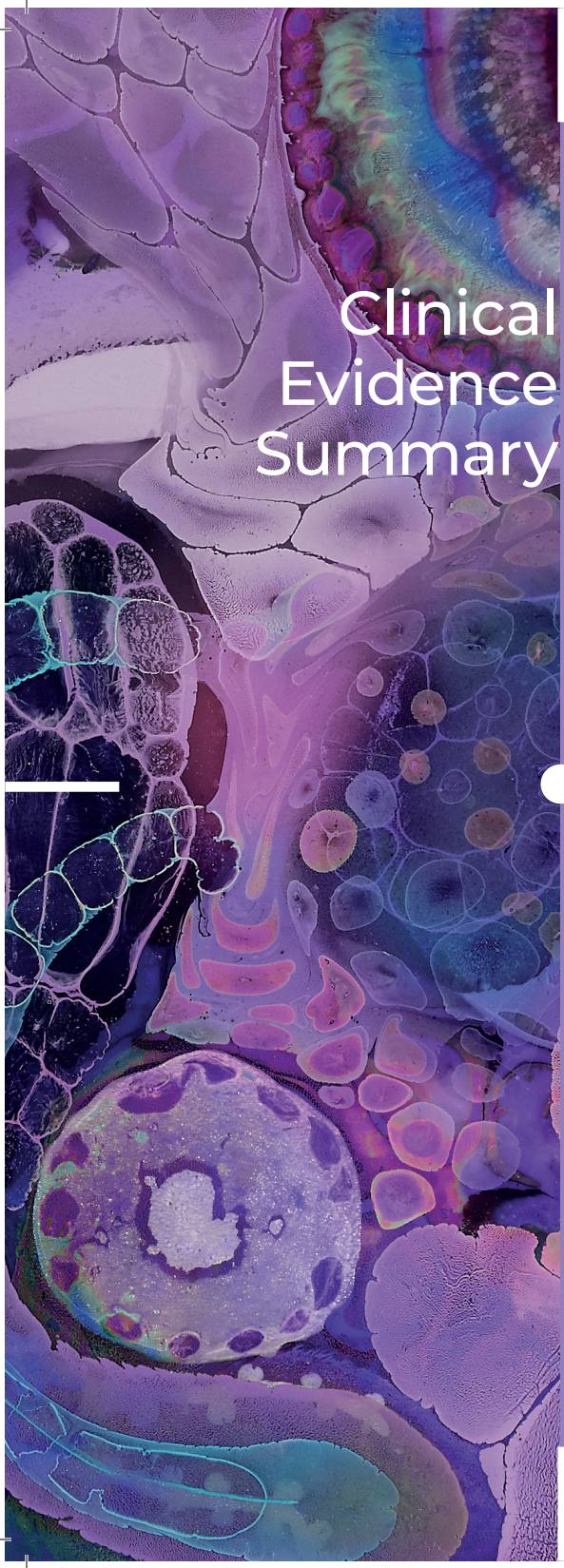
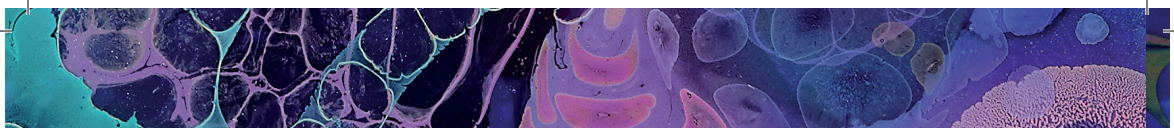


Precision Biotics

Clinical Evidence Summary

Stress & the 1714™ Probiotic Strain



CLINICAL EVIDENCE SUMMARY

Stress & the **1714**™ Probiotic Strain

Key Points

- Stress is common and an everyday part of life, but over time can negatively impact physical and mental health[1-3], placing financial strain on healthcare services[4].
- Regulation of the stress-response involves the gut-brain axis, which in turn may be regulated by the gut microbiota[5].
- Modulation of the gut microbiome with specific probiotic strains may therefore be a potential target to help manage everyday stress.
- Robust clinical and real-world research in healthy people has demonstrated that the *Bifidobacterium longum* **1714**™ strain leads to significant improvements in[6-8]:
  - ✓ Levels of perceived daily stress
  - ✓ Anxiety response following exposure to acute stress
  - ✓ Cortisol (stress hormone) output following exposure to acute stress
  - ✓ Brain wave activity during social stress which correlated with reduced feelings of distress - suggesting an improved ability to process and cope with stress
  - ✓ Feelings of stress, anxiousness and being overwhelmed
  - ✓ Sleep duration, difficulties falling/staying asleep and feelings of tiredness/fatigue
  - ✓ Overall wellbeing
- The **1714**™ strain has been carefully selected for its safety and efficacy, by PrecisionBiotics, who have over 20 years' experience of scientific research and expertise in this field.

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Mental Health and Stress

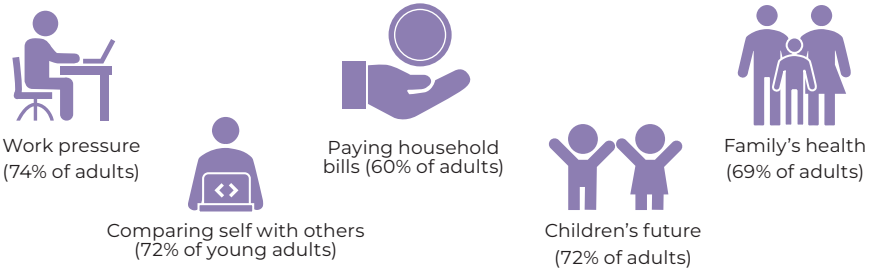
Research has revealed that mental wellbeing is the most commonly cited indicator of good health amongst individuals when asked what being healthy means to them[9].

> *"Mental health is a state of mental well-being that enables people to cope with the stresses of life, to realize their abilities, to learn well and work well, and contribute to their community. It is an integral component of health and wellbeing and is more than the absence of mental disorder."*
>
> **World Health Organisation (2022)[2]**

Mental health exists on a spectrum and is influenced by many factors, including exposure to everyday stress[2]. Feeling stressed is common amongst the general U.K. population, with research reporting that[3,10]:

- 74% of people have felt so stressed that they have been unable to cope
- 82% of people feel stressed at least some time during a typical week
- Of people who feel stressed, 51% report feeling depressed and 61% report feeling anxious
- 79% of employees report moderate-to-high levels of stress

Multiple aspects of everyday life contribute towards feelings of stress with the most commonly reported including[2,3,11]:



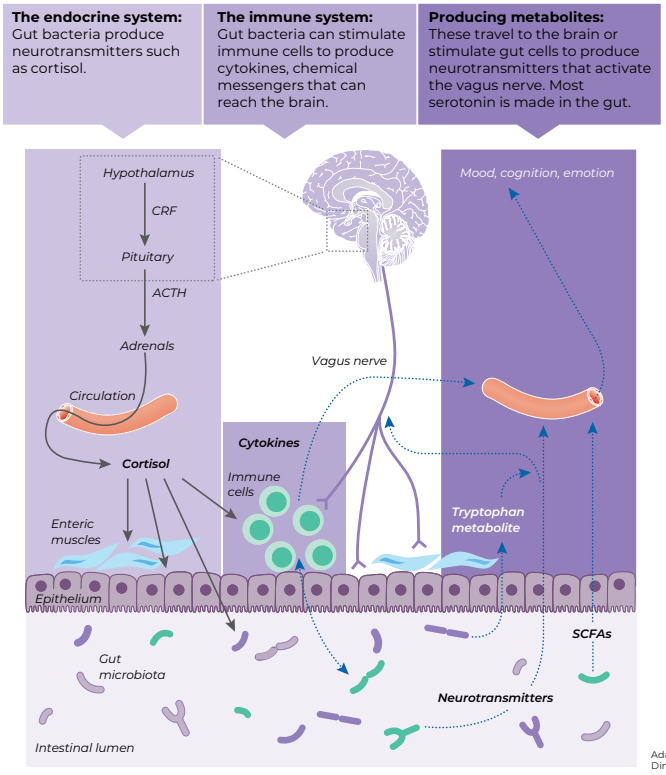
While stress is a normal aspect of life, exposure to high levels of stress over a prolonged period of time can have negative implications for both mental and physical health[1-3]. Stress has been recognised as a risk factor for a number of physical conditions including gastrointestinal, cardiovascular, and musculoskeletal[2,4]. Globally, stress-related health issues are estimated to account for 25% of hospital admissions, 19% of emergency department attendances, 35% of primary care visits and 12% of outpatient attendances per year[4]. Empowering people to embrace lifestyle strategies to prevent and manage everyday stress is increasingly important.

The Gut-Brain Axis

The importance of the gut–brain axis in regulating stress-related responses has long been appreciated. The gut-brain axis is the bidirectional communication pathway between the gut and the brain[5]. It is a complex regulatory system involving the central nervous system, enteric nervous system (our 'second brain' which controls the function of our gastrointestinal tract), as well as the endocrine and immune systems[5]. The functions of the gut-brain axis include coordinating gut functions and connecting the emotional centres of the brain with peripheral intestinal functions and mechanisms, including enteric reflex, intestinal permeability, immune activation and enteroendocrine signalling[12].

The Microbiota-Gut-Brain Axis

In recent years, the gut microbiota has emerged as a key regulator of the gut-brain axis, also known as the **microbiota-gut-brain-axis**[5,13]. The gut microbiota can communicate with the brain via[5,14]



Adapted from Cryan and Dinan (2012)[14]

For example, the gut microbiota produce short chain fatty acids which may increase the integrity of the blood brain barrier, limiting undesirable metabolites reaching the brain[12]. Other compounds produced by the gut microbiota (such as lipoproteins and lipopolysaccharides) may stimulate the release of cytokines from immune cells, which cross the blood brain barrier and activate neurons which influence neurological function, mood and behaviour[12].

Not only does the gut microbiota influence the stress response through these systems, but in turn stress may influence the profile of the gut microbiota[14,15]. The gut microbiota should therefore be considered as a potential target in the management of stress. Recent studies have demonstrated that interventions that modulate the gut microbiota can help to manage stress via the gut-brain axis[13,14].

Probiotics in Stress Management

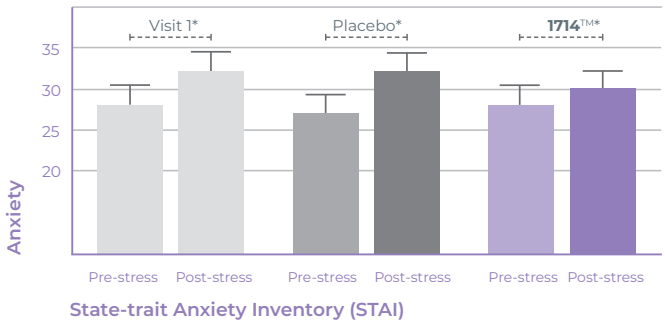
Emerging evidence has demonstrated the benefits of probiotics as a strategy for managing everyday stress[6,7,16,17].

The effects of probiotics are strain specific, and relatively few have demonstrated evidence of efficacy in stress. *Bifidobacterium longum* **1714™** has demonstrated a number of positive effects related to stress in pre-clinical, clinical and real-world research. This is summarised below.

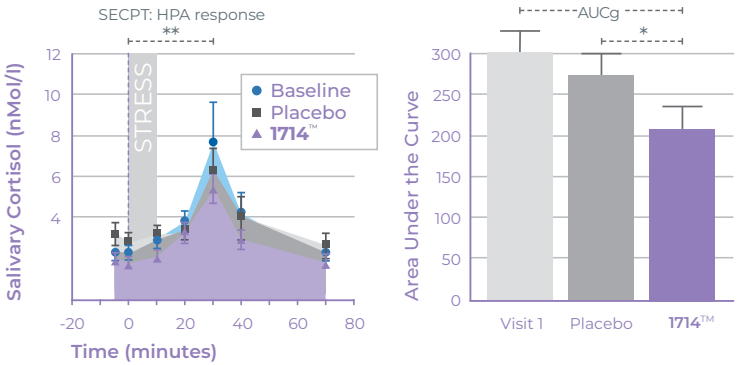
Benefits of the *Bifidobacterium longum* 1714™ Strain – Clinical Research

Clinical trials[6,7] comparing the **1714™** strain to placebo in healthy people have demonstrated significant benefits including:

- Attenuation of anxiety levels following exposure to acute stress[6]
  Anxiety significantly increased ($p<0.01$) in those taking placebo, but not in those taking the **1714™** strain.



- Significantly lower cortisol (stress hormone) output following exposure to acute stress ($p<0.05$)[6]

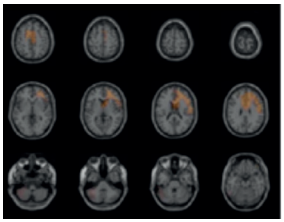


- Significantly lower levels of perceived daily stress ($p=0.03$)[6]

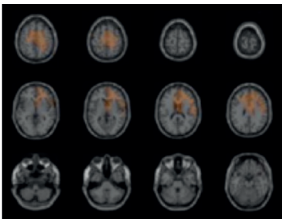
*p<0.05 **p<0.001

- Significant increases in theta ($p<0.03$) and alpha ($p<0.05$) brain wave activity during social stress.

  This correlated with reduced acute distress scores ($p=0.008$)[7]



Orange shading: increased theta wave activity with the **1714**™ strain vs placebo.

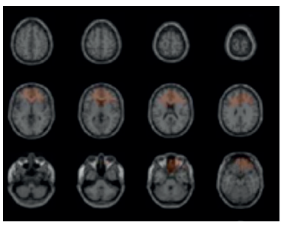


Orange shading: increased alpha wave activity with the **1714**™ strain vs placebo.

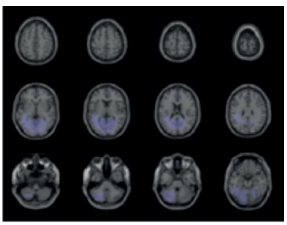
- These results could suggest the **1714**™ strain helps to manage stress by modulating brain activity in a way that activates coping centres within the brain to[7]:
  - Improve the ability to process stress
  - Making it easier to cope with stress moderating brain processes linked to negative emotions

- Significant increases in theta ($p<0.05$) and decreases in beta ($p<0.05$) brain wave activity at rest.

  This was associated with reduced mental fatigue and correlated with increased energy/vitality quality of life scores ($p\leq0.04$)[7]

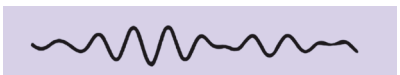


Orange shading: increased theta wave activity with the **1714**™ strain vs placebo.



Blue shading: reduced beta wave activity with the **1714**™ strain vs placebo.

Theta waves - induce release of a neurotransmitter (gamma-aminobutyric acid) which inhibits over-excitement[18]



Alpha waves, active during meditation and calmness[18]

Beta waves, high frequencies associated with feelings of agitation/anxiety[18]

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Benefits of the *Bifidobacterium longum* **1714**™ Strain – Real-World Evidence

In a real-world study conducted amongst hybrid workers (employees working in both office and remote settings), 10 weeks supplementation with the **1714**™ strain was associated with significant benefits compared to baseline including[8]:

- Improvements in feelings of stress – reported by 75% of participants. Feelings of stress occurred significantly less frequently (p=0.018) and less severely (not statistically significant)

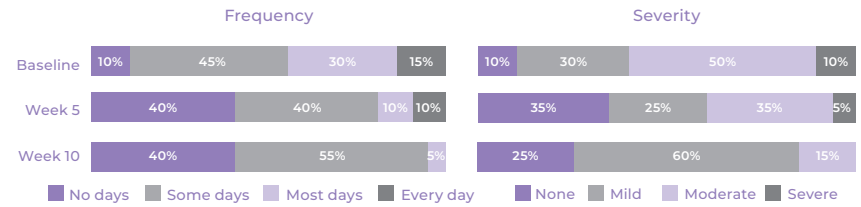

Figure. Likert scale scores for frequency and severity of feelings of stress, at baseline, week 5 and week 10 (percentage of participants)

- Improvements in feelings of anxiousness – reported by 75% of participants. Feelings of anxiousness occurred significantly less frequently (p=0.003) and less severely (p=0.038).

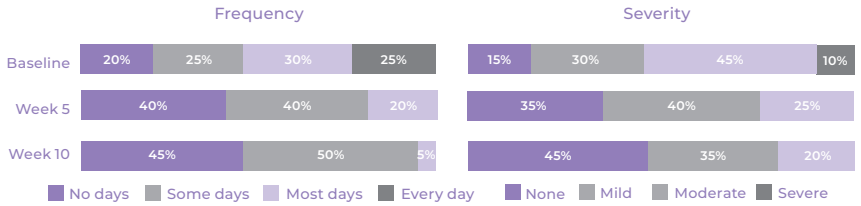

Figure. Likert scale scores for frequency and severity of feelings of anxiousness, at baseline, week 5 and week 10 (percentage of participants)

- Significant improvements in feelings of being overwhelmed, which occurred significantly less frequently (p=0.019) and less severely (p=0.008)
- Significant improvements in objectively measured mean sleep duration – by 20 minutes per night during the working week, compared to baseline on average (p=0.008)
- Significant improvements in the frequency and severity of feelings of tiredness/fatigue and difficulties falling and staying asleep (all p<0.05)
- Significant improvements in overall wellbeing - by 17% from baseline on average (p=0.005)

Overview of Research Methods

The efficacy of the **1714**™ strain has been assessed in two placebo-controlled clinical trials and one real-world study.

Clinical Trial 1: *Bifidobacterium longum* **1714** as a translational psychobiotic: modulation of stress, electrophysiology and neurocognition in healthy volunteers (Allen *et al*, 2016)[6]

A single-arm clinical trial of 22 healthy men. Participants consumed a daily placebo for 4 weeks, followed by a daily supplement with the **1714**™ strain at 1 x 10^9 (one billion) colony forming units (CFU) for 4 weeks, followed by a two week follow up period without probiotic supplementation. Perceived stress was recorded daily. At baseline, week 4 and week 8, anxiety after exposure to acute stress was measured and salivary samples were taken to measure cortisol output.

Clinical Trial 2: *Bifidobacterium longum* **1714™** strain modulates brain activity of healthy volunteers during social stress (Wang *et al,* 2019)[7]

A double-blind placebo-controlled randomised controlled trial of 40 healthy adults. Participants were randomised to receive either the **1714**™ strain at 1 x 10^9 (one billion) CFU, or a placebo, every day for 4 weeks. Outcomes measures included neural imaging at rest and during social stress, acute distress questionnaires and a validated quality of life survey (Short Form 36)[19], at baseline and week 4. Magnetic resonance images were taken on different days to provide a structural reference for the neural images.

MEG: magnetoencephalography (measures brain function through neuroimaging; CBG: Cyberball Game[20], a validated online social stress test; MR: magnetic resonance.

Real-World Study 1: Experiences of sleep, stress and wellbeing during 10 weeks of probiotic supplementation – a real-world study in hybrid workers. (Sorensen *et al*, 2024)[8]

A single-arm, open-label, real-world study of 20 hybrid workers (adults who worked in both office and remote settings). Participants received 10-weeks of daily probiotic supplements containing the **1714**™ strain at 1x10^9 (one billion) CFU and B-vitamins. Sleep duration was recorded with wearable devices. Online surveys (Likert scales) recorded the incidence and severity of sleep and stress related outcomes at baseline (1 week pre-supplementation), week 5 and week 10. Overall wellbeing was also measured at these time-points with a 10-point Likert Scale.

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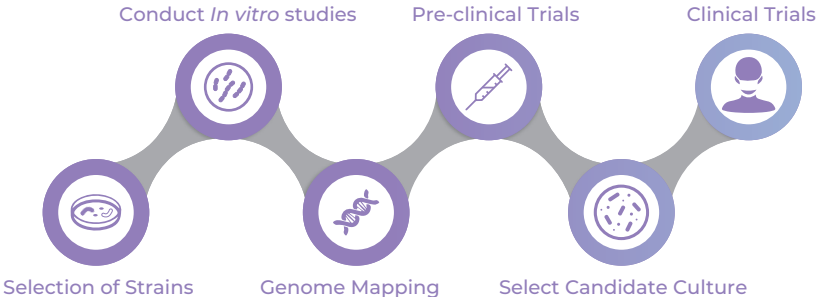
The Precise Approach to Probiotic Development

For over twenty years, PrecisionBiotics has discovered and developed unique probiotic strains in partnership with scientists and clinical experts from a world-leading centre of research into the microbiome and gut-brain axis - the APC Microbiome Ireland, University College Cork, Ireland. This follows a robust process to develop targeted probiotics:



The result is safe, effective, evidence-based probiotic supplements with targeted strains selected for their specific action in the specific condition.

Summary

Stress is common, with negative consequences for physical and mental health over the long term. Emerging evidence has highlighted the role of the gut microbiota in regulating the gut-brain axis. Clinical, pre-clinical and real-world evidence has shown that the **1714**™ strain may be effective at helping to manage everyday stress and reducing mental fatigue.

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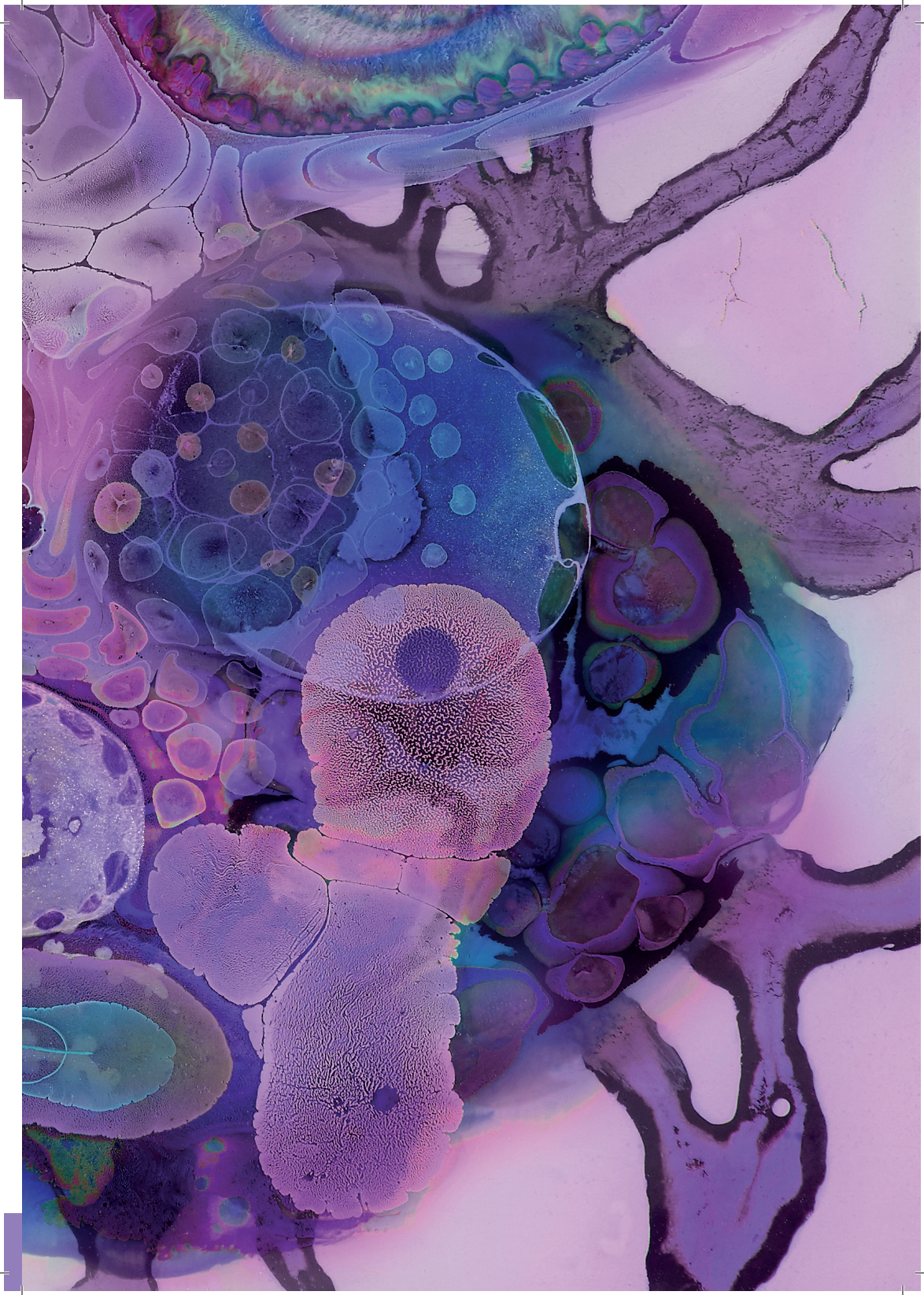

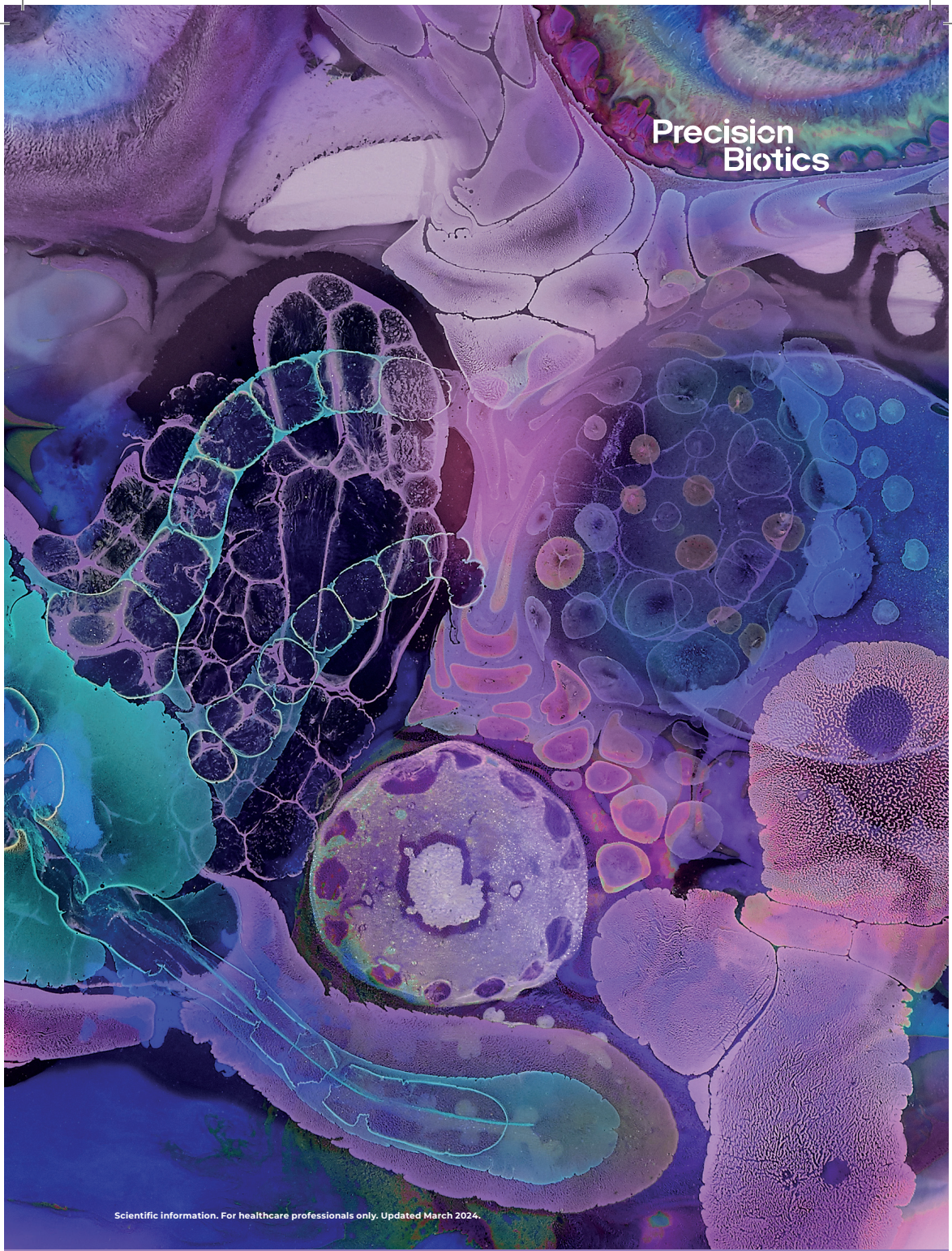

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