Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Photobiomodulation

Evidence Summary

Preclinical studies show PBM has the capacity to improve cellular function, but it is unclear if these effects can be robustly translated to humans. Clinical studies show good safety but modest efficacy.

Neuroprotective Benefit: tPBM may enhance brain bioenergetics, cerebral blood flow, and boost brain efficiency, but high-powered devices may be needed to modulate brain cells and produce durable responses. Optimal stimulation parameters are unclear.

Aging and related health concerns: PBM may help promote healing and alleviate pain, but, to date, it does not show clear utility for the prevention or treatment of major age-related health conditions.

Safety: PBM shows strong safety in clinical studies, with side effects generally limited to warmth or redness at the stimulation site. At-home LED-based devices are safe due to lower power. Extra protection and training are needed for clinic laser-based PBM.

Availability: In-clinic use, and at-home devices	**Dose**: Optimal stimulation parameters have not been established for any condition.	**Chemical formula:** N/A **MW**: N/A
Half-life: N/A	**BBB**: N/A	
Clinical trials: Hundreds of clinical trials have been conducted, testing PBM for different indications, most are small and underpowered and many lack adequate controls. The largest were the NEST-2 (n=660) and NEST-3 (n=566) trials of tPBM for stroke.	**Observational studies**: Data on long-term outcomes from participants receiving PBM is scarce.	

What is it?

Photobiomodulation (PBM), previously called low-level laser therapy (LLLT), involves the use of red (600 to 700 nm) or near-infrared (780 to 1100 nm) light to exert biological effects in cells or tissues [1]. While other wavelengths, such as those in the green light region (~500 nm), can also be used, and may show promise for some applications, the use of shorter wavelength PBM is still in relatively early stages and will not be covered in this report. PBM was originally discovered as mechanism to enhance wound healing, and its application has since expanded to treat a host of different conditions from musculoskeletal pain to brain injury. The biological mechanisms underlying protective effects have been demonstrated in cell culture systems and preclinical animal models. The primary mechanism is thought to involve the enhancement of mitochondrial function/energy production [1]. However, the degree to which this technique and these effects can be translated to humans has been difficult to assess. To date, the wide array of beneficial effects observed in preclinical studies have not been reliably replicated in humans. While evidence of clinical and physiological effects have been observed in human studies, the effects are inconsistent and much less robust than what is seen in preclinical models. This is expected to stem from variability in stimulation parameters and a lower capacity for light to reach affected tissues.

KEY CHALLENGE: The major limitation for the widespread use of PBM as a therapeutic intervention is the lack of standardization of stimulation parameters for any given condition. The issue is twofold. First, preclinical studies are inconsistent with respect to the stimulation parameters needed to elicit a particular physiological effect/promote tissue healing. Second, we currently lack a way to reliably measure the amount of light (energy) reaching the target tissue in a human patient. Animal model systems can utilize invasive procedures to deliver and measure light and downstream biochemical

effects which are not feasible in living human patients. This has led to a reliance on the use of postmortem tissue, which does not have the same optical properties as living tissue, and importantly lacks blood flow [2]. These experiments have generated estimates for the amount of light energy reaching a given tissue at different wavelengths and starting power densities.
Together, these studies support the notion that personalized, rather than standardized, stimulation parameters will ultimately be needed for PBM to have utility as a therapeutic intervention. The optimal wavelength and energy density may depend on the affected cell type, which may be impacted by the mitochondrial density of the cell type/tissue of interest [3], the composition of the tissue, in terms of different cell types, and which types one hopes to target with PBM. Since the activity of different cell types may be preferentially modulated by different wavelengths/energies of light, stimulation may result in variable effects across cell types, leading to variable outcomes/efficacy. Further research is needed to understand the key cell types of interest for different types of (tissue-healing) effects, and the light parameter range best suited to achieving those effects. Another important consideration is variability in stimulation site tissue properties across individuals, such as thickness, coloring, and water content. These features should be taken into account when determining the level of source light required to achieve the appropriate light energy at the target tissue in a given individual. However, without reliable ways to determine how much light is actually reaching the target tissue within a human, it will be difficult to determine clinically meaningful stimulation parameters.

While optimized stimulation parameters have not yet been established for any condition, model systems and simulations have provided some insight into key light properties and the ranges more likely to exert an effect in the target tissue.

Light wavelength: Shorter wavelengths of light have higher energy, while longer wavelengths have lower energy, but greater capacity to penetrate tissue, leading to a trade-off. As a result, red light (600-700 nm) is typically used for the treatment of superficial tissues, such as skin, whereas near-infrared light (780 to 1100 nm) is used for deeper tissues [3]. The wavelength range of 700 to 770 nm is avoided due to a lack of biological activity, likely due to poor absorption by biologically active chromophores coupled with higher absorption by non-active chromophores. Another key consideration is the wavelength absorption range of key biologically active chromophores. The one considered to be most relevant for PBM is cytochrome C oxidase (CCO), located in the inner membrane of mitochondria, which has four redox-sensitive metal ion chromophores (two heme-iron and two copper) [1]. PBM targets the oxidized state of CCO, which has absorption peaks around 680 nm and 825 nm for the copper ions [4]. Research suggests that the wavelength range of 810 to 830 nm is most effective for activating CCO

within tissue, likely due to low absorption by other molecules, such as water, and strong absorption by CCO, in that range. However, due to greater penetration capacity, some studies have found that longer wavelengths (such as 1064 nm) may be better suited for stimulation of deep tissues, like the brain [5]. Physiological effects are observed with longer near-infrared wavelengths, but the active chromophores mediating these effects are not yet clear [4]. Some studies suggest that a dual wavelength approach, such as the use of a higher energy red with a deeper penetrating near-infrared, may offer greater efficacy than a single wavelength alone, perhaps by being able to engage different cell types and/or processes simultaneously [2].

Light source: An area of controversy in the field relates to the utility of light-emitting diodes (LEDs) compared with lasers as the stimulation light source [6]. One difference is the type of light generated. Lasers produce coherent light, while LEDs produce non-coherent light [6]. Coherent light waves are synchronized in frequency, while non-coherent light waves out of phase with one another, resulting in light scattering. Some studies suggest that when the coherent light interacts with tissue, it creates interference patterns called laser speckles which may have higher capacity to stimulate mitochondria [6]. Lasers also allow for higher peak power, which may be important for deep tissue targets [2]. However, high powered lasers are expensive and pose safety risks, and thus are not suitable for home use. LEDs, on the other hand, are inexpensive and safe, such that they can be organized into arrays to target larger areas, and amenable for home use devices [6]. Some researchers contend that lasers offer superior results, but overall, the field remains divided, and lacks a clear consensus. Whether one modality offers a clear advantage may depend on the target tissue and indication. Head-to-head studies are needed.

Frequency: A more recent consideration is the use of a pulsed light at a particular frequency, relative to continuous light. The majority of studies have used continuous wave light, so it is clear that, at least experimentally, PBM can achieve biological effects with a continuous light source. However, more recent studies suggest that pulsed light may offer better outcomes, particularly when targeting deep tissues, such as the brain [2]. The use of pulsed light can allow for higher powered light sources but with stimulation at a lower amount of time, to allow for more light energy to reach the tissue while avoiding damage. Pulsed light also appears to be able to penetrate deeper than continuous light. Within the brain, the use of pulsed light can also potentially be used for the entrainment of brain waves at particular frequencies [7]. However, research in this area indicates that the effects are quite complex, and may be difficult to predict. The impact of pulsed light on brain waves appears to depend on light wavelength, such that combinations of different frequences (such as 10 Hz or 40 Hz) with different

wavelengths of light (such as 810 nm or 1064 nm) may have different effects on different types of brain waves, and in some cases opposing effects [7; 8].

Power output/Irradiance/Fluence: Perhaps the most important feature is the energy intensity of the light stimulation [3]. The light delivered to the tissue is impacted by the peak power delivered by the light source, which is measured in Watts (W), the size of the stimulation site (measured in cm^2), and the time of exposure (measured in seconds). These allow for the calculation of the critical features of power density or irradiance, and the radiant energy exposure or dose, also called the fluence [3].
The power density/irradiance refers to the amount of light power delivered to the stimulation site, and is impacted by the power of the light source and the size of the stimulation area (W/cm^2).
The radiant exposure/fluence refers to the amount of light energy delivered to the stimulation site, and is impacted by the power density and the duration of time [calculated as power density (W/cm^2) X time (s) to produce fluence J/cm^2]. This is arguably the most important measure for determining the potential biological effect of the light [2; 3].

PBM exhibits a biphasic dose response, also known as the Arndt–Schulz law, in which at very low levels there will be no effect, at moderate levels there is a stimulatory effect, and at high levels there is an inhibitory effect [1]. High levels of light energy may damage the tissue, promoting oxidative stress and inflammation, rather than inhibiting them. Thus, it is important that the light energy level falls within the therapeutic window.
Recommended power densities typically range from 1 to 100 mW/cm^2, though studies suggest that when targeting the brain, power densities of 75 to 250 mW/cm^2 may be needed [2; 3; 8]. Fluence levels of 3 to 10 J/cm^2 show evidence of metabolic activity at the cellular level [3]. However, these refer to direct light energy for relatively superficial targets. For deeper targets, higher fluences are typically needed, generally in the range of 10 to 50 J/cm^2, while for exposed open wounds, lower levels (<1 J/cm^2) may suffice [3].
It is also important to note that the distribution of the light energy across the tissue surface will not be uniform, but instead follow a distribution pattern with cells in the center of the light source receiving higher irradiation and cells in the periphery receiving only a fraction of the light power [3]. This power density distribution, in turn, produces a fluence distribution, which affects the probability that cells within the stimulation site will absorb meaningful amounts of light energy. Thus, the energy distribution can be greatly impacted by the spot area at the tissue level, such that at a given power output, differences in spot areas may result in power densities and distributions lower than intended.

Since fluence is a byproduct of both power density and time, a particular fluence can be achieved using high power for a short period of time or low power for a long period of time [3]. A key caveat is that if the power density is too low then even with infinite time, the light energy will be insufficient to have a biological effect. Therefore, this relationship between power density and time only works within a particular range of the dose curve (i.e. the therapeutic range) [3].
Some researchers provide evidence to suggest that many of the low power LEDs used in home devices are below the level that would allow for any light to reach the brain [2]. Furthermore, when within the power range where light may penetrate to the brain, the duration of light exposure, typically around 20 or 30 minutes, is far below the duration, typically in the order of hours, that would be needed to deliver a meaningful fluence to the brain tissue [2].

Fluence at tissue level: The stimulation parameters provide information about the light energy delivered to the tissue surface (such as the skin) but not necessarily to the intended target of interest. Instead, it can only be estimated based on the properties of the overlying tissue. Research suggests that a fluence level between 0.9 J/cm^2 to 15 J/cm at the level of the target tissue is needed to have a meaningful effect at the cellular level [2]. The amount of light scattered/reflected depends on the optical properties of the tissue, as well as the thickness. Overlying tissue can include hair, skin, fat, bone, connective tissue, and blood vessels, which each have their own light scattering properties [2]. Melanin is a chromophore, thus skin pigmentation can affect the level of light penetration, with greater light penetration with lighter skin tones (i.e. less melanin) [5]. Similarly, hair, which also usually contains melanin, is a major barrier to light penetration [2]. As a result, stimulation site placement is critical for maximizing light penetration to target tissues. With respect to the brain, most studies utilize sites on the forehead, targeting the frontal/prefrontal cortex [2]. Meaningful light levels would not be expected to reach the brain with devices that have stimulation sites on the head that are covered with hair. Skin and skull thickness can also vary across individuals, and could play a role in efficacy [2].
Studies suggest that near-infrared light (around 1 to 3%) may be able to penetrate 1 to 5 mm into the brain, to have direct cellular effects, but only with high enough fluences [2]. Research to date suggests that high powered lasers (10 to 15W) may be needed to penetrate through the various tissue layers (skin, skull, meninges) into the brain at meaningful energy levels [2].

Neuroprotective Benefit: tPBM may enhance brain bioenergetics, cerebral blood flow, and boost brain efficiency, but high-powered devices may be needed to modulate brain cells and produce durable responses. Optimal stimulation parameters are unclear.

Types of evidence:

- 1 meta-analysis on studies testing tPBM for cognitive performance in healthy adults
- 3 additional clinical trials tPBM for cognitive performance in healthy adults
- 7 studies assessing brain biomarkers of laser tPBM in healthy adults.
- 1 review of clinical studies testing tPBM for brain conditions
- 4 small, controlled trials, including biomarker outcomes, testing tPBM in AD
- 3 RCTs (NEST trials) testing tPBM for stroke
- 1 systematic review of clinical trials testing PBM in Parkinson's disease
- 4 clinical trials testing PBM in PD
- 2 systematic reviews of clinical trials testing tPBM for TBI
- 2 pilot clinical trials testing tPBM for TBI
- 1 clinical study testing tPBM for TBI/depression
- 2 meta-analyses of clinical studies testing tPBM in depression
- 1 RCT (ELATED-3) testing tPBM for major depressive disorder
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

There is evidence to support the capacity of transcranial photobiomodulation (tPBM) to enhance cognitive function in healthy adults, though the durability of the effects is not clear, and likely depends on the specific stimulation parameters.

Evidence of cognitive effects

A meta-analysis including six studies assessing the impact of tPBM on cognitive performance in healthy young adults found that tPBM was associated with improved cognition-related outcomes with a standardized mean difference (SMD) of 0.833 (95% confidence interval [CI] 0.458 to 1.209) [9]. The cognitive outcomes involved attention, memory, and executive function. The studies were relatively small in size, ranging from 30 to 118 participants, and the overall quality score of the included studies was modest, indicating that these results should be taken with caution. These studies tested only a

single session of tPBM, so the frequency required for a sustained effect is unclear. Another study not included in the meta-analysis, but which used similar parameters (1064 nm, irradiance 0.167 W/cm^2, fluence 120 J/cm^2) with a continuous wave laser (Model JL-LS-100, Jieliang Medical Device), also found that tPBM to the right prefrontal cortex improved visual working memory capacity in healthy young adults [10]. Notably, in this study, a similar effect was not observed when the stimulation used a different wavelength (852 nm) that is also within the range considered to have biomodulatory effects, suggesting that there may be some specificity to biological responses achieved at different stimulation parameters.

A key challenge in these types of analyses is heterogeneity in the stimulation parameters. There is reason to believe that the biological processes impacted by PBM are influenced by the stimulation parameters, with a key aspect pertaining to the amount of light that actually reaches cells within the brain. In this meta-analysis, most of the studies used similar stimulation parameters (see table below), namely a light wavelength of 1064 nm laser (Model CG-5000 Laser, Cell Gen Therapeutics) at continuous wave mode, power output of 3.4 W, irradiance of 250 mW/cm^2, fluence of 60 J/cm^2, targeted to the frontal cortex/prefrontal cortex (typically the FP2 site) [9]. Based on studies indicating that around 2% of 1064 nm light can pass through the supraorbital frontal skull, it is expected that superficial cortical neurons would receive a fluence (radiant energy) around ~1.2 J/cm^2, which is within the range (0.9 J/cm^2 to 15 J/cm^2) that is expected to be biologically meaningful [2].

Device	Model	Wavelength	Power	Irradiance	Fluence	Estimated fluence at brain surface (assuming 2% penetrance)
Laser continuous wave	CG-5000, Cell Gen Therapeutics	1064 nm	3.4 W	250 mW/cm^2	60 J/cm^2	1.2 J/cm^2

Biomarker evidence of physiological effects

Furthermore, several studies assessing brain activity using electroencephalography (EEG), near-infrared spectroscopy (NIRS), and magnetic resonance imaging (MRI) provide evidence that these stimulation parameters (or similar parameters with a higher fluence also within the range of expected biological activity in the brain) have acute effects on neural activity and brain blood flow.

NIRS provides indirect information about hemodynamics (blood flow) by measuring the light absorption of the oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HHb) [11]. It can also be used to provide information about cellular metabolism, by measuring changes in the redox state of the mitochondrial protein cytochrome oxidase C (CCO) [11]. When combined, this technique can provide information about metabolic-hemodynamic coupling. In general, increased cellular metabolic activity would be expected to drive blood flow to that region. tPBM, using the CG-5000 Laser with previously described parameters and fluence of 110 J/cm^2, has been shown to increase the change in CCO oxidation (indicative of increased neural activity) and increase the level of oxygenated hemoglobin (indicative of an increase in cerebral blood flow) to stimulated regions based on broadband NIRS [11].

Studies utilizing functional NIRS (fNIRS) have found that tPBM (CG-5000 Laser with previously described parameters and fluence of 120 J/cm^2) can modulate cerebral activity related to vasomotion, which is related to spontaneous, rhythmic oscillations in vascular tone derived from the blood vessel wall [12; 13]. A study that used similar stimulation parameters (described above) but a different laser source (CNI laser-MIL-N-1064, China) found that tPBM increased nodal efficiency and functional connectivity in brain networks in healthy older adults based on resting-state fNIRS, and that this enhancement of network efficiency was associated with better working memory performance based on the 3-back task [14].

EEG can be used to measure electrical activity in the brain. Prefrontal tPBM stimulation has been shown to modulate brainwaves, which are rhythmic waves of neural (electrical) activity in the brain [15]. These occur at different frequencies, with delta waves representing the lowest frequency occurring during slow-wave-sleep, and gamma waves occurring at the highest frequency and associated with learning and attention. One study found that tPBM (using the CG-5000 Laser with previously described parameters and fluence of 120 J/cm^2) enhanced alpha and beta waves during a resting state, and that these effects were distinct from thermal-mediated effects on neural activity [15]. One concern of studies assessing the effects of PBM is that the assessments could be affected by changes that may occur simply by heating the tissue.

Another study using the EVO FX Tri-wavelength Class-4 Therapy Laser (1064 nm, power output of 0.6 W for 11 minutes directed to vertex of cranium) found that tPBM increased activity in the somatomotor region of the brain in the context of a finger-tapping task based on blood oxygenation level dependent (BOLD) functional MRI (fMRI) [16]. Additionally, there was a trend toward increased structural and functional connectivity between the motor cortex and thalamus, based on structural and functional MRI measures in response to tPBM. These stimulation parameters are expected to reach brain cells at a

biologically meaningful level, though the placement of the stimulation site in a region of the head that typically contains hair may have impacted the penetration of light.

The studies described above provide evidence that tPBM administered via a continuous wave laser at a wavelength of 1064 nm and estimated fluence to the cortical surface >0.9 J/cm^2 can modulate electrical activity in the brain, blood flow, and cognitive performance in healthy adults.
However, light in the range of 810 to 830 nm is largely considered to be optimal for tPBM due to capacity for penetration to the brain and targeting of mitochondrial enzymes [2], and studies suggest that brain activity is also subject to modulation from tPBM in the 800 nm range. For example, one study found that 800 nm tPBM to the prefrontal region at an irradiance of 0.25 W/cm^2, and fluence of 120 J/cm^2) affected brain network activity based on EEG [17]. Notably, the research group that conducted this study is one of the groups that has demonstrated effects on brain activity and blood flow with tPBM using 1064 nm light.

Brain effects observed in studies with low light power
Meanwhile, other studies have been conducted that report positive effects on cognition, but which use stimulation parameters that provide a light energy output (fluence) that is below the level that is thought to be needed to modulate activity within brain cells [2]. There is debate about the efficacy of LED light relative to laser light for tPBM, but the source may not be as important as the power output [3]. A key criticism of LED-based studies is that the power output of the LED is too low to achieve a biologically meaningful fluence level [2]. In these cases, it is thought that tPBM could still impact the brain, however, under these conditions, the impact would be related to systemic effects (i.e. remote PBM) rather than direct modulation of brain cells [2]. It is expected that the systemic-driven effects would be less durable.

There are fNIRS studies to support that tPBM, when delivered at these lower energy levels, can modulate brain hemodynamic responses. Based on preclinical studies, one of the protective systemic effects of PBM is expected to involve changes in blood flow [4]. One research group has conducted several studies with low power LED devices (see table below for parameters) and found that tPBM resulted in reduced oxygenated hemoglobin responses on fNIRS following a difficult cognitive task in young and older healthy adults, suggestive of enhanced cognitive efficiency [18; 19]. However, the change in hemodynamic response was not reliably associated with better task performance in the older adults [19]. One study found that, when fluence remained below the level experts consider to be within the range that can affect the brain, increasing it did not provide additional benefit [20]. This is consistent

with mechanisms related to a systemic effect. In comparison to studies with expected brain penetration, low power tPBM may result in more variable, less durable responses that are more impacted by baseline cognitive status and brain health. More studies are needed to directly compare low and high power tPBM on brain function.

Device	Wavelength	Power	Irradiance	Fluence	Estimated brain fluence (assuming 2% penetrance)
LED Continuous Wave	810 nm	60 mW	20 mW/cm^2	7 J/cm^2	0.14 J/cm^2

Human research to suggest benefits to patients with dementia:

A variety of small studies have been conducted testing PBM, most commonly tPBM, in dementia patients [21]. Many of the studies report benefits to measures of cognition and sleep. However, most of these studies do not include effects on disease-associated biomarkers or markers of brain function, such as network activity. In addition to lacking statistical power, many studies also lack robust controls, which hinders interpretability of the effects. There is a lot of heterogeneity across the studies in terms of the stimulation parameters, such that without these biomarker measures it is difficult to make objective comparisons, which are needed to determine the optimal stimulation parameters for different types of dementias.

Clinical trials are currently underway that include more brain function-related measures, which may provide more information regarding the clinical utility of tPBM for patients with dementia.

A randomized, double-blind, placebo-controlled trial tested tPBM in 93 adults with mild cognitive impairment (MCI), 76 of which completed the study [22]. Participants received 24 sessions (three times per week) over the course of 60 days utilizing dual wavelength light, with red light (660 nm, irradiance 10 mW/cm^2, fluence 12 J/cm^2) and near-infrared light (850 nm, irradiance 23 mW/cm^2, fluence 27.6 J/cm^2) administered for 20 minutes per session. This low power of light would not be expected to deliver biologically meaningful amounts of light into brain tissue, suggesting any benefits may be related to systemic effects. The study found that tPBM resulted in better cognitive performance on the Montreal Cognitive Assessment (MoCA) relative to placebo, which was accompanied by an increase in serum levels of BDNF. No significant effects on measures related to mood or neurodegeneration biomarkers were observed.

The TRAP-AD study is randomized, sham-controlled trial testing tPBM in patients with amnestic mild cognitive impairment (MCI) and early AD (CDR of 0.5-1; FAST 1-4; age 65-85) (NCT04784416) [23]. The study plans to enroll 125 participants. The primary outcome is the change in Repeatable Battery for the Assessment of Neuropsychological Status Update (RBANS) Total Scale Index Score. Brain tau levels, brain bioenergetics, and functional connectivity will also be measured using,18F MK-6240, 31P-MRS, and fMRI, respectively. In this study, tPBM is administered via the Transcranial PhotoBioModulation-1000 (t-PBM-2.0) device (LiteCure). The helmet is configured to deliver pulsed laser diode light at/near the EEG sites F4 and F3 at a wavelength of 808 nm and frequency of 42 Hz. The device will deliver an average irradiance: 277.8 mW/cm^2, and exposure time of 667 s (~11 minutes), resulting in a fluence of 185.3 J/cm^2. Based on an estimated light penetration of 2%, the expected fluence reaching brain tissue would be about 3.7 J/cm^2, which is well within the biologically active range. The study has an expected completion date in 2026. This study is expected to provide insight into the utility of tPBM for modulating brain function in AD patients.
To date, an analysis of fractional amplitude of low-frequency fluctuations (fALFF), a technique that indicates variation in intrinsic brain activity based on variations in blood oxygen level-dependent (BOLD) signals, has been conducted in 19 participants [24]. Changes in fALFF in sites of the frontal cortex, such as F1, F2, and F3 were observed in response to tPBM. Notably, the responses were more robust during the session than afterwards. The study authors suggest that this technique may be useful for assessing target engagement and optimization of stimulation parameters/diode placement for tPBM studies.

A pilot trial including eight patients with mild-to-moderate dementia, tested the effect of at-home tPBM for 12 weeks in comparison to standard care [25]. Stimulation was administered via the Vielight Neuro Gamma device three times per week, with the assistance of the study partner/caretaker. The device delivers 810 nm light pulsed at a frequency of 40 Hz. Transcranial LEDs are located anteriorly and posteriorly, providing irradiances of 75 mW/cm^2 and 100 mW/cm^2, respectively. The device also contains an intranasal LED providing an irradiance of 25 mW/cm^2. The stimulation sessions were 20 minutes in duration, resulting in fluences of 60, 45, and 15 J/cm^2 for the posterior, anterior, and intranasal sites, respectively. These stimulation parameters would be expected to deliver a meaningful amount of light energy to brain cells (see table below).
Participants treated with tPBM showed trends toward improvements on the ADAS-Cog and Neuropsychiatric Inventory (NPI) after 12 weeks, while performance declined in the standard care group. Increased cerebral blood flow was also observed in those treated with tPBM.

Device	Model	Wavelength	Power	Irradiance	Fluence	Estimated brain fluence (assuming 2% penetrance)
LED Pulsed 40 Hz	Vielight Neuro Gamma	810 nm	25/75/100 mW	25/75/100 mW/cm^2	15/45/60 J/cm^2	0.5 to 1.2 J/cm2

A pilot, randomized, sham-controlled, feasibility study tested tPBM in 14 patients with mild cognitive impairment (MCI) [26]. Participants received stimulation using the Vielight Neuro RX Gamma device once per day for six weeks. There were trends toward cognitive improvements on the trail-making B test and the MMSE favoring the active tPBM group. Biomarker analysis showed some evidence of improved metabolic function with tPBM. Levels of blood biomarkers related to mitochondrial health, butyrate and L-carnitine, increased with tPBM. Changes in functional connectivity in the default mode network and increased right thalamic volume were also observed.

A trial that aimed to test the Vielight Neuro Gamma in 228 patients with moderate to severe AD was suspended due to slow enrollment (NCT03484143).

Prevention trial: The Vielight intranasal device is being tested in combination with two MedX Rehab Console systems (MedX Health, 1116 and 3MedX MCT502) in 168 older adults at risk for AD in a double-blind, randomized, sham-controlled Phase 2 trial (NCT04018092). The MedX systems will deliver light via LED cluster (irradiance 22.2 mW/cm^2, treatment area of 22.48 cm^2) transcranially with an energy density of 1 $Joule/cm^2$ in 45 seconds, using a wavelength of 870 nm. The LED cluster has an irradiance of 22.2 mW/cm^2 and treats an area of 22.48 cm^2. The Vielight device will deliver 810 nm light intranasally pulsed at a frequency of 10 Hz, with an irradiance of 7.6 mW/cm^2 for 25 minutes. Laboratory sessions will involve a total of 40 minutes of stimulation over a total of 16 sites, while intranasal stimulation (25 minutes/day) will also be performed at home, over the course of 12 weeks. The primary outcome is the change on ARENA, a computer-based task of spatial memory-navigation. Imaging measures will be assessed as secondary outcomes, including cerebral mitochondrial function (31P MRS ATP) and resting state functional connectivity (rs-fMRI). The study has an expected completion date in 2026.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Mitochondrial: The primary mechanism by which PBM is proposed to modulate physiological processes is by affecting the redox state of the mitochondrial enzyme cytochrome oxidase C (CCO), also known as Complex IV, which is the last enzyme in the respiratory electron transport chain involved in the production of cellular energy in the form of ATP [1] . CCO contains four redox-active metal ion centers, two heme iron centers and two copper ion centers. The oxidation-reduction state of these centers impacts the conformation state of the enzyme, influencing its catalytic activity, and thus the rate of production of ATP [4]. These metal ion centers in CCO have absorption peaks in the red region of the light spectrum, including 605 nm, 620 nm, 655 nm, and 680 nm, as well as in the near-infrared part of the spectrum, including 760 nm and 825 nm [4]. The absorption of the photon energy excites the electrons in these metal centers, which is expected to promote the production of ATP, though the exact mechanisms by which light affects CCO activity are not fully understood [4]. In addition to CCO, light energy may affect other mitochondrial enzymes with redox-active metal ions. There is evidence to suggest that while not optimal for CCO, 1064 nm light can impact the activity of a variety of enzymes along the mitochondrial respiratory chain, possibly leading to similar functional outcomes [2]. However, the particular enzymes impacted may depend on the wavelengths, which could lead to different downstream biological effects. Additionally, longer wavelengths of near infrared light may instead be absorbed by water, which has an absorption peak around 970 nm [27]. A change in vibrational energy from a water cluster could lead to changes in protein conformation, for example opening a heat-ion gated channel (TRP channel) or enhance the efficacy of ATP synthase in mitochondria [27].

Signaling: The absorption of light energy (photons) by CCO and other mitochondrial enzymes leading to changes in redox status, is expected to result in the generation of reactive oxygen species (ROS) [1; 28]. ROS play important roles in cellular signaling, including pathways involved in cell growth and survival, including MAPK and PI3K/AKT. This may result in the induction of cell growth factors, such as BDNF. At low levels ROS can promote the upregulation of antioxidant enzymes which may help alleviate oxidative stress. It is important, however, that the stimulation intensity is not high enough to damage tissue, which would instead induce high levels of ROS and promote oxidative stress damage [3]. Some studies suggest that the optimal tissue fluence for ROS modulation is about 3 J/cm^2. The modulation of mitochondrial activity resulting in increases in ATP levels and the release of calcium ions (Ca^2+) can also affect downstream cell signaling. Chromophores in non-mitochondrial proteins could also potentially impact signaling. For example, TRPV channels, which play a role in various sensory responses such as temperature and pain, may have light-sensitive activity, though evidence suggests it is in the green part of the light spectrum. Therefore, it would be expected that different wavelengths of light could differentially activate various cell signaling pathways.

Neuroinflammation: As part of its ability to impact cellular signaling, PBM shows the capacity to modulate the expression of inflammatory mediators [27]. PBM has been shown to modulate the NF-kB signaling pathway, and reduce expression of downstream pro-inflammatory cytokines, such as TNF-α, IL-β, and IL-6 [27]. In preclinical studies, PBM has shown the ability to modulate the activation state of monocytes/macrophages [27].

Hemodynamics: In conjunction with a boost in cellular bioenergetics, PBM can boost cerebral blood flow [4]. Human studies have found that changes to brain activity patterns following PBM, precede changes in blood flow, indicative of metabolic-hemodynamic coupling [11]. PBM may also promote vasodilation and enhancement of blood flow via activation of nitric oxide (NO), a potent vasodilator [4; 28]. Light energy absorption by CCO may trigger the release of CCO-bound NO, which serves to activate both CCO respiratory activity and downstream NO-mediated signaling [28]. PBM has also been shown to enhance NO bioavailability from intracellular stores via other heme chromophore-containing proteins [29]. Longer wavelengths of near-infrared light with less impact on CCO, have also been shown to activate NO in endothelial cells via modulation of mitochondrial activity [29].

Sleep/Glymphatic: Preclinical studies in rodents provide evidence that tPBM can facilitate the clearance of waste products and misfolded proteins from the brain via the glymphatic system [21; 30]. The drainage capacity of the meningeal lymphatics into the cervical lymph nodes in aged mice was enhanced following tPBM, which was accompanied by improved cognitive performance [30]. Similarly, tPBM has been shown to enhance the clearance of pathological proteins from the brain via the meningeal lymphatics in AD models [30]. Some studies indicate that adenosine signaling plays a role in the activation of the glymphatic system [31], suggesting that changes in mitochondrial activity may be involved in the glymphatic effect. Due to difficulties in directly assessing glymphatic function in humans, we do not yet have clear evidence of whether tPBM can elicit a similar effect in humans [4], particularly since the level of light penetration is much lower across the human skull relative to rodents. However, the clearance of metabolic waste products from the brain via the glymphatic system is most active during deep (slow wave) sleep, and several clinical studies report improvements in sleep with tPBM [21]. The potential degree of deep sleep enhancement with tPBM is not yet clear.

Remote/Systemic PBM

Biological effects have been observed in clinical studies using stimulation parameters with light intensities below the level expected to reach/activate target tissues. Preclinical studies suggest that

stimulation to non-target tissues, for example to the leg in the context of a brain disease model, can also produce meaningful physiological effects [32; 33]. This is typically referred to as remote PBM, and in contrast to the local targeted tissue effects of direct PBM, remote PBM involves systemic effects. Rodent studies have found that remote PBM can alter gene expression in the brain [32]. Pathway analysis suggests that a key mechanism of remote PBM may involve the proliferation and mobilization of stem cells from the bone marrow, particularly mesenchymal stem cells, which are then recruited to sites of damage throughout the body [32]. Remote PBM may also promote vascular health, such as enhancing the integrity of the BBB. Another possibility is that remote PBM induces similar signaling pathway activation as direct PBM through the activation of circulating cell-free mitochondria [4]. While the respiratory capacity of these cell-free organelles remains unclear, photon absorption may still trigger actions leading to the release of signaling molecules, such as ROS, calcium, and adenosine. These messengers could then influence downstream signaling pathways in a non-cell autonomous manner, resulting in systemic effects. Research suggests that the effects of remote PBM may be less durable, requiring regular sessions for meaningful effects [2]. Remote PBM is still not well understood, with many outstanding questions. For example, the degree to which the location of the stimulation site matters is unclear, including whether there may be a bias in the types of effects (e.g. stem cell mobilization vs anti-inflammatory signaling) depending on the site [32]. The impact of stimulation parameters on the induction and durability of remote PBM effects is also unclear.

Clinical studies using tPBM for brain injury and neurodegenerative disease

Stroke: NO CLEAR BENEFIT IN TRIALS WITH LOW LIGHT POWER
tPBM has been most robustly tested in the context of acute ischemic stroke through the NeuroThera® Effectiveness and Safety Trial (NEST) trials [28]. These randomized, double-blind sham-controlled trials used the class IV NeuroThera Laser System (PhotoThera, Inc., dissolved following failure of NEST-3 trial) with treatment occurring within 24 hours of stroke. In the NEST-1 trial (n=120), more participants receiving tPBM experience successful outcomes at day 90 relative to those receiving sham (70% vs 51%) [34]. The NEST-2 trial (n=660) did not meet its primary outcome, as similar numbers of participants achieved favorable outcomes by day 90 between the tPBM and sham groups (36.3% vs 30.9%) [35]. Participants with lower NIHSS scores, indicative of less neurological impairment, were more likely to show benefit from tPBM. tPBM had no meaningful effect on infarct volume in this study [36]. The Phase 3 NEST-3 trial was terminated for futility based on analysis including 566 participants indicating no significant difference in the percentage of patients with a good functional outcome with tPBM compared to sham (49.6% vs 49.3%) [37]. Experts in the field suggest that the negative results stem

from tPBM stimulation parameters below the level that is expected to reach the surface of the brain at biologically meaningful levels (see table below). The degree of benefit is also expected to be impacted by the depth of the infarct, such that deeper brain tissue would not receive enough light for a direct effect.

Device	Model	Wavelength	Irradiance	Fluence	Estimated fluence at brain surface (assuming 2% penetrance)
Laser continuous wave	NeuroThera	808 nm	10 mW/cm^2	1.2 J/cm^2	0.024 J/cm^2

The benefits observed with tPBM in preclinical models of stroke have not been reliably observed in human stroke patients to date [38]. The fluence (amount of light energy) reaching the brain is likely to be a key factor accounting for the translational differences. Due to the smaller head size of animal models, such as rodents and rabbits, more light is able to penetrate into the brain and reach the site of the infarct [38]. It has not yet been determined whether light needs to penetrate to the level of the site of the infarct/tissue damage to have a clinically meaningful effect on stroke recovery. If this is the case, then it is likely stroke patients may differentially benefit from tPBM depending on the location of the infarct, and the optimal stimulation parameters may vary from patient to patient. The use of non-personalized stimulation protocols may have contributed to the lack of consistent benefit in the clinical studies thus far. The results from the NEST trials suggest that some patients may receive modest benefits from mechanisms related to remote PBM, but that these responses are inconsistent and may not meaningfully impact clinical trajectories.

Parkinson's disease: NO CLEAR BENEFIT ON MDS-UPDRS/ MOTOR FUNCTION TO DATE
There have been several case studies, but limited controlled clinical trials testing PBM in patients with PD [39]. A key challenge for the use of tPBM is that the predominant brain regions affected, such as the substantia nigra, are located deep within the brain making them inaccessible to light administered to the head [39]. To try to enhance light penetration, some studies also utilize intranasal or intraoral PBM stimulation. Preclinical studies in PD models suggest that remote PBM may also have neuroprotective effects [39]. Consequently, some studies have also incorporated remote PBM stimulation to other parts of the body into their design. However, it could be argued that if tPBM parameters are unable to reach PD affected brain regions then studies using tPBM are effectively also testing a type of remote PBM.

To date, PBM has not been able to offer meaningful benefit on the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III, which is the gold standard for assessing motor function in PD patients. Stimulation parameters offering clinically meaningful benefit have not yet been established.

One small, sham-controlled RCT (NCT03811613) testing tPBM in 35 patients with PD using an LED-based system with power output of 60 mW/cm^2 and fluence (radiant energy) of 8 J/cm^2 estimated that a radiant energy of 0.09375 J/cm^2 would reach the cortex, while only a radiant energy of 0.009375 J/cm^2 would likely reach the substantia nigra pars compacta [40]. Participants received 18 tPBM sessions using a wavelength of 670 nm (red range) administered in six one-minute blocks over the course of nine weeks. While there was an increase in gait speed, improvement was not observed on a variety of other motor outcomes, consistent with limited light energy reaching brain regions involved in motor control.

A double-blind, randomized, sham-controlled trial in 22 PD patients tested 50 Hz pulsed PBM administered via laser along the cranium and intra-orally (along palate), with a power of 60 mW per diode, energy of 2 J per point, and a wavelength of 904 nm (infrared range), parameters expected to reach at least superficial regions of the brain, once, twice, or thrice per week for four weeks [41]. Trends toward improvement on fine motor measures were noted with higher frequency sessions, but no significant effects were observed. The study authors suggest that longer treatment may be needed for benefit.

A proof-of-concept study used a waitlist design, in which six patients with idiopathic PD (Hoehn and Yahr stage I, II) received transcranial, intranasal, neck and abdominal PBM for 12 weeks, while another six patients received the same treatment after a 14-week waiting period [42]. The study used a combination of devices, including the LED VieLight Neuro Gamma device to deliver 810 nm light transcranially (pulse 40 Hz, irradiance 75 or 100 mW/cm^2 per diode, fluence 90 or 120 J/cm^2) and intranasally (pulse 40 Hz, irradiance 25 mW/cm^2, fluence 30 J/cm^2), as well as the class I SYMBYX PDCARE Irradia laser device (904 nm, pulse 50 Hz, irradiance 47 mW/cm^2 per diode) to deliver light transdermally to the C1/C2 region of the neck and to the abdomen. Based on these stimulation parameters, it would be expected that a meaningful amount of light could reach brain cells at the cortical surface, but it is unlikely meaningful amounts of light would reach deep brain structures. PBM was administered three times per week during weeks 1 to 4, then two times per week during weeks 5 to 8, and to once per week during weeks 9 to 12. At the end of the 12 weeks, participants were given the devices for at home use three times per week for 25 or 40 weeks. Improvements were observed on mobility, motor, and cognitive measures that were maintained for at least a year with sustained

treatment [42]. However, improvements were also observed prior to treatment in the waitlist group. Without a true placebo group, it is difficult to assess the impact of treatment. Notably, less improvement was observed during the down-titration period to fewer weekly sessions suggesting that the durability of the response wanes over time, necessitating regular treatment sessions. The composition of the gut microbiome was not significantly changed, but trends toward phyla changes associated with better gut health, such as the Firmicutes to Bacteroidetes ratio were observed [43]. This could potentially be related to the PBM directed toward the abdomen.
A five-year follow-up including six participants that continued home treatment, found that improvements observed by the first year relative to baseline were largely maintained for motor and cognitive measures, but they did tend to gradually decline or plateau, and did not show further improvement with prolonged treatment sessions [44]. This suggests there may be a limit to the neuroprotection that can be achieved from PBM due to the progressive nature of PD. MDS-UPDRS-III scores were not significantly affected by PBM treatment [44].

A double-blind, randomized, sham-controlled feasibility trial in 40 idiopathic PD patients tested an LED-based tPBM helmet (SYMBYX Pty Ltd) containing 40 LEDs using either 635 nm (red; power 27 mW for 12 min, fluence 5.4 J/cm^2) or 810 nm (infrared; power 52 mW for 12 min, fluence 10.4 J/cm^2) light six days per week for 12 weeks [45]. These stimulation parameters would not be expected to deliver meaningful amounts of light energy to the brain. There were no significant differences between tPBM and sham on the MDS-UPDRS-III scores in this study [45; 46].

Traumatic brain injury (TBI): POTENTIAL BENFEIT
Evidence from case reports and small clinical studies suggests that tPBM may have utility for TBI depending on the nature of the head injury, when administered in an individualized manner [47]. A key challenge is heterogeneity in affected brain regions across individuals, such that some patients may be better candidates for PBM than others. Some studies suggest that higher powered pulsed stimulation with the capacity to modulate brain network activity has the greatest potential utility of TBI.

A systematic review of six studies all using LED-based tPBM for chronic TBI found that there was wide variation in the stimulation parameters used across studies in terms of pulsed vs continuous wave, stimulation sites, irradiance, and fluence [48]. Most used dual (red/infrared) wavelength stimulation (629 to 633 nm and 850 to 870 nm), though some used only one wavelength, with most sessions lasting 20 minutes. In all cases, light fluence (radiant energy) was lower than would be expected to

meaningfully affect brain cells. Improvements in cognitive function were noted, but without randomization or controls, the meaningfulness or consistency of these results is unclear.

One research group indicated improvements in a case series of 10 patients with mild to moderate chronic TBI using a class IV high-power NIR laser in symptoms of headache, sleep disturbance, cognition, mood dysregulation, anxiety, and irritability following 10 sessions or 20 sessions. Nine of the 10 TBI patients received tPBM with a dual-wavelength (810/908 nm) NIR laser (LT1000, LiteCure; 10W, pulsed at 10 Hz) with a fluence ranging from 55 J/cm^2 to 81 J/cm^2 [49]. Based on these parameters, they expected a radiant energy of 0.8 to 2.4 J/cm^2 to reach into brain tissue, 3 cm from stimulation source. This research group has conducted several studies assessing the penetration of light using different stimulation parameters, and found that the use of high-powered lasers with a pulsed frequency allows for deeper penetration into deep tissue, which may be required to reach damaged brain tissue in the context of brain injury [49]. This group has also found that this stimulation paradigm can lead to durable benefits for depression in TBI patients (see depression section below).

A randomized, double-blind, sham-controlled RCT (NCT02233413) tested three 20-minute tPBM sessions (at least 12 hours apart) in 68 patients with acute, nonpenetrating, moderate TBI starting 72 hours after injury using a custom-built helmet containing 18 clusters of 20 NIR LEDs (810 nm, irradiance 36 mW/cm^2, fluence 43 J/cm^2) [50]. Based on the assumption of 3% of incident light reaching the cortical surface, the study authors estimate that the radiant light energy reaching brain cells to be 1.3 J/cm^2, which would be in the biologically meaningful range. However, this is likely to be an overestimate of the fluence within the brain, with many studies finding light penetration across the head closer to 1 or 2% [2]. Additionally, the helmet distributes light over regions that are typically covered by hair, which dramatically reduces the penetration of light due to scattering and absorption [2].
Symptom severity was not significantly impacted by the tPBM relative to sham treatment. The study included MRI measures related to white matter integrity, and found time-dependent effects on diffusion parameters (diffusivity and fractional anisotropy) in the late sub-acute phase [50].

A non-randomized proof-of-concept trial tested the effect of tPBM plus intranasal PBM in 49 patients with a history of repetitive head acceleration events for 8 to 10 weeks using the Vielight Neuro gamma (v3) at-home device [51]. The device contains four 1 cm^2 LEDs along the scalp targeting the midline dorsomedial prefrontal cortex (irradiance 75 mW/cm^2, fluence 45 J/cm^2), lateral parietal areas (irradiance 100 mW/cm^2, fluence 60 J/cm^2), and the midline precuneus (irradiance100 mW/cm^2, fluence 60 J/cm^2), as well as one intranasal LED (irradiance 25 mW/cm^2, fluence 15 J/cm^2). Based on these

stimulation parameters, it is expected that some light would reach the brain surface at meaningful levels. However, affected brain regions are likely to vary from patient to patient, thus it is unclear the degree to which a meaningful amount of light would reach affected brain regions in a given individual. The light was pulsed at a frequency of 40 Hz, with sessions lasting 20 minutes administered every other day. Using the reliable change index, a statistical tool to determine the significance of individual score changes over time, between 0 to 36% of participants showed meaningful change on cognitive measures, including the NIH Toolbox Cognition Battery, depending on the particular test [51]. Resting state fMRI data from a subset of 30 participants indicated changes in network connectivity [52].

Depression: POTENTIAL BENEFIT

The etiology of depression is not well understood, and likely varies amongst patients. Impairments in brain energy metabolism have been observed in the context of depression, suggesting a role of mitochondrial dysfunction [53]. Based on the proposed mechanism that PBM can improve mitochondrial function and enhance energy production, tPBM has been tested in the context of major depressive disorder [53]. As is the case for conditions targeting the brain, it is important for sufficient light to reach brain areas of interest. With depression, the most relevant brain regions to target are not clear, though some may be deep subcortical/limbic regions which may be difficult to access using tPBM. A common stimulation site for depression is the dorsolateral prefrontal cortex, likely due to its accessibility for non-invasive stimulation techniques. The uncertainty over the target sites may account for some of the variability across studies. Stimulation parameters also vary across studies.

Clinically beneficial stimulation parameters for depression have not yet been validated. Studies conducted to date suggest that systemic or low-power PBM may offer temporary benefits, but higher powered stimulation capable of reaching into deeper brain structures may be needed for a meaningful and durable response [2].

A meta-analysis of eight studies including 102 participants found that tPBM showed efficacy in relieving symptoms of depression in single-arm studies, but the effects were not significant relative to sham in controlled trials [54]. The authors conclude that dose-finding studies are needed to optimize tPBM parameters for depression.

A separate meta-analysis of 11 RCTs including 407 participants found that PBM was effective in reducing depressive symptoms relative to controls (SMD: -0.55, 95% CI -0.75 to -0.35), while sleep symptoms were not significantly affected based on an analysis of two trials including 57 participants [55]. They indicate that studies using systemic PBM showed greater efficacy than those using tPBM for depression.

Since inflammation is also implicated in depression, systemic PBM may be acting through an anti-inflammatory mechanism.

The randomized, sham-controlled ELATED-3 trial tested low power tPBM (830 nm; LiteCure TPBM-1000 continuous wave laser; treatment area 35.8 cm^2; average irradiance 54.8 mW/cm^2; average fluence 65.8 J/cm^2; ~2 W total power, total energy 2.3 kJ per session) administered in 20-minute sessions bilaterally to the prefrontal cortex twice per week for six weeks in patients with major depressive disorder [56]. An analysis including 49 participants found that tPBM had no significant effect on depressive symptoms based on the Hamilton Depression Rating Scale (HDRS-17) and Quick Inventory of Depressive Symptomatology-Clinician Rating (QIDS-C) scores. The study authors conclude that the light level (irradiance, energy per session) was too low, thus a minimum dose is likely required for a therapeutic effect. Due to the low power, any light reaching the brain would likely remain at a superficial level and be unable to meaningfully penetrate into deeper brain layers. They note that two of the stimulation sites had potential interference from hair, which would have significantly diminished the light level reaching into the brain. This study suggests that light may need to reach deeper brain regions to have a therapeutic effect, which may be achieved using higher power stimulation.

A single arm study tested high-power tPBM for the alleviation of depression symptoms in 39 patients with chronic mild to moderate TBI using a class IV dual wavelength (810/980 nm) 10 W laser (LT1000, LiteCure), 15 W 810nm Diowave laser, or 15 W 810 nm/980 nm Aspen Laser, all of which can deliver continuous or pulsed light [57]. The fluence at skin level ranged from 55 to 81 J/cm^2, with an average of 16.8 ± 6.26 treatment sessions per participant. Based on light penetration studies conducted by this research group, they estimated that 0.8–2.4 J/cm^2 of light energy would reach within 3 cm of brain tissue. Following treatment, QID scores fell from 14.10 ± 3.39 (moderate depression) to 3.41 ± 3.30 (no depression). Similar effects were observed on the Hamilton Depression Scale. Thirty-six participants exhibited a decrease in depressive symptoms, while 32 participants showed evidence of remission, based on QID scores falling into the 'no depression' (<5) range. The effects appeared to persist for at least a year, with some participants reporting benefit out to 55 months (~4.5 years). While lacking a comparator group, this study provides support for the notion that high power tPBM with the capacity to penetrate into deeper brain layers may be needed to provide durable benefit for depression with this technique.

APOE4 interactions: It has not yet been established whether ApoE4 status affects the efficacy of tPBM. However, since the presence of ApoE4 is associated with impaired mitochondrial function [58], ApoE4

carriers may be expected to preferentially benefit from tPBM, due to its proposed mechanism of boosting mitochondrial activity.

Aging and related health concerns: PBM may help promote healing and alleviate pain, but, to date, it does not show clear utility for the prevention or treatment of major age-related health conditions.

Types of evidence:

- 1 umbrella meta-analysis of PBM for various health conditions
- 1 meta-analysis of trials testing PBM for skin wounds
- 1 network meta-analysis of trials testing PBM for orthodontic procedures
- 3 meta-analyses of trials testing PBM for knee osteoarthritis
- 1 meta-analysis of trials testing PBM for rheumatoid arthritis
- 1 meta-analysis of trials testing PBM for tendinopathy
- 1 meta-analysis of trials testing PBM for carpal tunnel syndrome
- 1 systematic review of trials testing PBM for maxillofacial neuropathies
- I meta-analysis of trials testing PBM for chemotherapy-induced neuropathy
- 1 review of trials testing PBM for age-related macular degeneration
- Numerous laboratory studies

Healing: POTENTIAL MODEST BENEFIT
In terms of clinical utility, PBM has the most extensive history for the use of wound healing [3]. Skin healing is expected to be the process most amenable to PBM intervention due to the proximity of the light source to the site of injury. As a result, it may be expected that optimal stimulation parameters for skin wound healing would have been established. However, a consensus has yet to emerge [3]. This may stem from differences across wounds, in terms of cause, location, depth, and severity. Analyses of clinical studies suggest that some types of wounds may be more amenable to PBM-based therapy than others.

A meta-analysis of RCTs examining 670 skin wounds, including ulcers, burns, and skin graft donor sites found that, overall, the wound size was reduced to a greater extent in PBM treated wounds (MD: 25.84%, 95% CI 13.93 to 37.70), with high heterogeneity across the results [59]. The rate of complete wound closure was also statistically greater with PBM. Interestingly, this analysis found that wound closure rates were not related to wavelength or the laser energy density, which ranged from 1 to 10

J/cm^2. A prior analysis found a biphasic response in terms of energy density, such that energy densities in the range of 19 to 24 J/cm^2 showed greater efficacy than those at higher (>130 J/cm^2) or lower (<8.25 J/cm^2) levels [60]. PBM also shows greater efficacy in wound healing in animal models, relative to human studies [60].

The efficacy in terms of healing and pain reduction varied across wound types, such that ulcers showed evidence of benefit, whereas episiotomy (i.e. childbirth-related) wounds did not benefit from PBM [59]. An umbrella review including 15 meta-analyses from 204 RCTs (>9,000 participants) assessing 35 health endpoints found a protective effect of PBM for the healing of diabetic foot ulcers, but with a low certainty of evidence [61].

Mechanism: Based on preclinical studies, PBM is proposed to promote tissue healing through modulation of the inflammatory response and the induction of repair processes, such as production of growth factors and blood vessels and the mobilization of stem cells [1]. Preclinical studies have found that PBM can promote the differentiation and mobilization of stem cells, such as mesenchymal stem cells (MSCs), through the induction of cell signaling pathways involved in cell proliferation and survival [62]. While direct stimulation may allow for the induction of local repair process, studies suggest that effects on inflammatory mediators and stem cell mobilization are systemic effects, and thus can potentially be achieved through remote/systemic PBM [4; 32]. To date, it is not clear the degree to which these different mechanisms promote healing in humans, or the degree to which the stimulation parameters influence the induction of these various processes. As such, optimal stimulation parameters have not yet been established.

Pain

PBM shows evidence of anti-nociceptive properties in preclinical models [63]. Increases in pain thresholds were accompanied by changes in neurotransmitter activity in dorsal root ganglia and along nerve fibers in rodents [63]. Another potential mechanism involves the reduction of inflammatory mediators, which may help with the alleviation of inflammation-related pain [63].

Orthodontic/dental: POTENTIAL BENEFIT

A growing area of the use of PBM is for dental and orthodontic procedures. Studies suggest that it can help alleviate pain and inflammation associated with tooth movement, without hindering the process [64]. There is some evidence that it may assist with bone remodeling and accelerate tooth movement. To date, evidence of PBM's effects on bone remodeling and tissue repair are largely restricted to preclinical animal studies, with human studies primarily focused on the use of PBM for pain management following orthodontic/dental procedures [64]. Similar to other conditions, the key

question pertains to the optimal stimulation parameters, such as the irradiation required to reach the tooth root as well as the energy density at the level of the tooth root required to exert the desired effects, such as bone remodeling/ tissue healing [64].

A network meta-analysis assessing the pain relief capacity of PBM (16 studies) relative to ibuprofen (9 studies) following orthodontic separator placement found that the two interventions showed relatively comparable efficacy, with slightly better pain reduction at 6 hours with ibuprofen and slightly better efficacy at 24 hours with PBM [65].

Knee osteoarthritis: POTENTIAL BENEFIT FOR PAIN BUT NOT FUNCTION
Clinical studies generally find that PBM shows benefits for reducing pain relative to knee osteoarthritis, while it shows a lower efficacy regarding joint stiffness and functional capacity, relative to other interventions.
A network meta-analysis of 13 RCTs ranging in size from 19 to 101 participants, including a total of 673 participants with knee osteoarthritis found that PBM showed greater efficacy than sham stimulation for pain relief (SMD: 0.96, 95% CI 0.31 to 1.61), particularly when longer wavelengths of near-infrared light (~904 nm) were used [66]. The longer wavelengths allow for greater tissue penetration, which may allow for a greater fraction of light to reach the affected tissue, and thus greater efficacy. In contrast to pain, PBM did not show significant benefits for measures related to knee stiffness or function.
Similarly, a network meta-analysis including 139 clinical studies assessing 10 interventions for knee osteoarthritis found that PBM was one of the more effective therapies in terms of pain relief, whereas it ranked much lower in terms of efficacy for function/stiffness [67].
Meanwhile, a separate network meta-analysis including 32 clinical studies assessing six interventions for knee osteoarthritis found that PBM was one of the most effective therapies for both joint pain, and function [68]. However, the types of interventions differed from the prior analysis, with many of the included interventions showing low efficacy, which may have inflated the apparent efficacy of PBM.

Rheumatoid arthritis: In contrast, to osteoarthritis, clinical studies have not found PBM to be effective for the treatment of rheumatoid arthritis. A meta-analysis of 18 RCTs including 793 participants found that PBM, using either red or near-infrared light, had no significant effects on pain, stiffness, or functional capacity [69]. The included studies primarily applied light to affected joints in the hand. The difference in apparent efficacy for the different types of arthritis may be related to different etiologies, and degree of localization. Osteoarthritis tends to be localized to particular joints, whereas rheumatoid arthritis is a systemic autoimmune condition, thus PBM may be able to promote tissue repair within the

targeted joint, but would have less capacity to alleviate the underlying systemic autoimmune dysfunction.

An umbrella review including 15 meta-analyses from 204 RCTs (>9,000 participants) assessing 35 health endpoints found a protective effect of PBM for knee osteoarthritis for pain and disability with low to moderate certainty of evidence, but no effect for rheumatoid arthritis [61].

Tendinopathy: POTENTIAL MODEST BENEFIT
A meta-analysis of 35 controlled clinical studies found that PBM was modestly beneficial in providing pain relief for chronic tendinopathy relative to minimal intervention, with benefits more apparent with more frequent PBM sessions [70].
An umbrella review including 15 meta-analyses from 204 RCTs (>9,000 participants) assessing 35 health endpoints also found a protective effect of PBM for pain in the context of tendinopathy with a low certainty of evidence [61].

Neuropathy: POTENTIAL MODEST BENEFIT FOR SOME SUBTYPES
Mitochondrial dysfunction and inflammation are implicated in the development of peripheral neuropathy. As such, PBM has been proposed to offer utility for neuropathy by enhancing mitochondrial function and energy production, as well as reducing inflammatory mediators [71]. The induction of growth factors, such as NGF and BDNF, and neural repair processes has also been observed in preclinical animal models.
To date, clinical studies show modest effects for PBM. Depending on the location and underlying etiology, some neuropathies may be more amenable to PBM intervention than others. Due to heterogeneity across studies, it is not yet possible to identify 'optimal' stimulation parameters for the treatment or prevention of neuropathy.

Maxillofacial neuropathies: A systematic review of 18 RCTs, including 1,220 patients with maxillofacial neuropathies from studies ranging in size from 25 to 150 participants, found that PBM was associated with a reduction in pain score on the visual analog scale (VAS) (mean reduction: -3.5, 95 % CI -2.8 to -4.2) with the greatest efficacy observed in studies targeting trigeminal neuralgia [72]. The recovery of sensory thresholds was accelerated by 45%, particularly in patients undergoing surgical procedures, based on six RCTs. Wound healing rates were accelerated by 25%, in studies using 810 nm PBM.
In terms of stimulation parameters, higher energy densities (15–20 J/cm^2) were more efficacious for chronic neuropathy, while benefits for sub-acute conditions, such as post-surgical recovery, could be

achieved with energy densities as low as 2 to 5 J/cm². Similarly, longer wavelengths (800–900 nm) with greater tissue penetration potential were most effective for deeper tissue targets, while higher energy shorter wavelengths (630–700 nm) worked well for superficial targets.

Ulnar neuropathy at the elbow includes symptoms of pain, weakness, and loss of feeling in the lower arm. An RCT (n=68) testing PBM found that it enhanced treatment outcomes relative to splinting alone. PBM was associated with improvements on measures of pain and sensory nerve conduction velocity, but was not superior to sham on measures related to weakness, grip strength, or electrophysiology [73].

Carpal tunnel syndrome involves compression of the medial nerve in the wrist, resulting in pain, numbness, and weakness. Analyses suggest that, at least under parameters that have been tested thus far, PBM may only offer marginal benefit for carpal tunnel syndrome.
A meta-analysis of 13 RCTs assessing 735 wrists examined the efficacy of PBM for carpal tunnel syndrome [74]. There was considerable heterogeneity across studies in terms of stimulation parameters, and the use of adjunctive treatments such as wrists splints and exercise. Included studies generally tested the impact of 10 to 20 PBM sessions. The meta-analysis found no significant effects for PBM on pain or handgrip strength, though there was a modest effect on functionality, as measured by Levine CTS Questionnaire and the Boston CTS Questionnaire (SMD: -1.18, 95% CI -2.06 to -0.30), which, at the higher end of the confidence interval, may be in the clinically meaningful range.
An umbrella review including 15 meta-analyses from 204 RCTs (>9,000 participants) assessing 35 health endpoints did not find evidence to support a clinical benefit of PBM for carpal tunnel syndrome [61].

Chemotherapy-induced peripheral neuropathy (CIPN): A systematic review of six trials including 273 patients with CIPN indicated heterogeneity of stimulation parameters across studies, with wavelengths ranging from 630 nm to 905 nm, including dual and single wavelength stimulation. Power densities and energy densities were not always reported [75]. A meta-analysis of four studies measuring neuropathy severity using modified total neuropathy score (mTNS), found a favorable effect for PBM (MD: -2.10, 95% CI -3.94 to -0.26) [75]. Similarly, a meta-analysis of four studies measuring neuropathy severity using FACT/GOG-NTX, also found an effect in favor of PBM (MD: -1.85, 95% CI -2.70 to -0.99) [75]. While directionally indicative of improvement, the magnitude of the effect was quite modest in most studies, such that they may not reach the level of clinical meaningfulness in most patients. It is possible that the irradiance and fluence levels may have been too low in most of the included studies.
For example, the study using the highest power density (300 mW/cm²) exhibited the greatest efficacy.

Treatment: The randomized, double-blind, sham-controlled cross-over trial included 70 patients with CIPN [76]. PBM was administered via 30-minute sessions three times per week for six weeks, using a K-1200 class 4 continuous laser (850 nm, irradiance 300 mW/cm^2, fluence 3 J/cm^2). All sessions targeted the lower part of the spine (lumbar-sacral), while the amount of the lower limb region (leg to foot) targeted decreased as the sessions progressed. Early sessions used a laser power of approximately 7 W, while later sessions targeting smaller regions used a laser power of 12 W. The study reported significant improvement (reduction) of neuropathy symptoms on the mTNS of -4.2 (-32.4%) at 4 weeks, -6.8 (-52.6%) at 8 weeks ($p<0.001$), and -5.0 (-38.8%) at 16 weeks with PBM, but no impact of sham (-0.1 [-0.7%] at 4 weeks to 0.0 [0.1%] at 16 weeks). Within the sub scores, the benefits were most apparent for sensory symptoms. Notably, this study did not find an additive or synergistic effect of combining PBM with physiotherapy.

Meanwhile, benefits observed in other PBM studies using lower power stimulation have been quite modest.
A Phase 2 randomized, sham-controlled, single-blind clinical trial tested PBM in 44 cancer survivors with established CIPN for at least three months [77]. The PBM was administered twice per week for 12 weeks using a class 2M diode continuous laser (Acupack CL Mini Laser) delivering 8 mW power at wavelength 658 µm through a 3.2-mm diameter aperture, at a dose of 1 Joule/point with dose escalation up to 2 Joule/point, as tolerated. The target sites included the interdigital spaces of the hands and feet (16 points), and sites corresponding to the C6-T1 and L5-S1 nerve roots bilaterally (10 points). Response rates (~50%) were similar between PBM and sham groups, with no complete responses. One notable difference was durability, in that symptom score improvements lasted longer in those treated with PBM.

Prevention: A randomized, sham-controlled (NEUROLASER) pilot trial tested the ability of PBM to prevent CIPN in 32 breast cancer patients undergoing chemotherapy [78]. Participants received stimulation using a dual diode class IV MLS M6 laser (ASA Srl, Italy), with wavelengths of 905 and 808 nm, peak powers of 25 W and 1.1 W, respectively. The treatment paradigm utilized a power density of 0.168 W/cm^2 and a fluence of 4 J/cm^2, with bilateral stimulation sites along the upper limbs, back, and lower limbs. There were no significant differences in neuropathy scores, though symptom severity tended to increase to a greater extent during the follow-up period in the control group.

Age-related macular degeneration: POTENTIAL BENEFIT
PBM has been tested in the context of non-neovascular AMD. The LIGHTSITE trials were sponsored by LumiThera [79]. Based on the results of these studies, the Valeda® light delivery device from LumiThera

received authorization from the FDA for vision treatment in patients with dry AMD. Patients in earlier stages showed the most benefit in terms of best-corrected visual acuity (BCVA) improvement [79]. The LIGHTSITE III trial demonstrated an improvement of 2.4 letters in vision between PBM relative to sham at 13 months, though the clinical relevance remains to be determined. PBM may help with disease stabilization/ slowing of progression in some patients, particularly at early stages.

Safety: PBM shows strong safety in clinical studies, with side effects generally limited to warmth or redness at the stimulation site. At-home LED-based devices are safe due to lower power. Extra protection and training are needed for clinic laser-based PBM.

Types of evidence:

- 2 reviews of stimulation parameters
- 2 simulation studies
- 10 clinical trials reporting safety outcomes
- Numerous laboratory studies

PBM has been found to be safe across a multitude of clinical studies applying stimulation to various different parts of the body. While many studies do not adequately address safety, most studies reporting safety outcomes find that side effects are rare, and are primarily limited to mild, transient discomfort at the stimulation site, such as warmth, redness, itching, or tingling [72; 80].
PBM has not been found to significantly affect measures of vital signs, or to negatively impact cognitive function [80; 81]. It has been safely used in a wide range of populations from healthy participants [80], to those with neurodegenerative disease, arthritis, open wounds, cancer, neuropathy, stroke, depression, or brain injury [15; 45; 61; 77; 78; 81; 82]. However, caution is warranted using PBM in cancer patients actively undergoing treatment due to potential impacts on cell growth and proliferation. To date, clinical studies have not found evidence of malignant transformation from PBM [78; 83].

The major concern for PBM is for high-intensity light-related tissue damage [2]. The power intensity of devices cleared for home use, which are typically LED based, is generally below the level that could cause tissue damage, even with prolonged use. The greater concern with these devices is that the power may be too low to be efficacious for deep tissue targets. In contrast, high powered lasers, such as Class 4 lasers pose a real safety risk. Stimulation parameters must be carefully calibrated to prevent excessive heating or damaging the tissue at the stimulation site. As a result, these types of procedures should only

be conducted in clinical settings with highly trained experts. Eye protection should always be worn in the presence of high-power lasers.
Modeling studies provide guidelines for upper limit safety thresholds, such that the skin-exposure safety limit of Class 3B and 4 near-infrared lasers ranges up to 500 mW/cm^2, depending on the wavelength and type of laser [5]. Power densities of 1000 mW/cm^2 or higher exceed both scalp and brain temperature safety limits [84]. The American National Standards Institute has established a power density safety limit of 330 mW/cm^2 [84].

Drug interactions: Photobiomodulation may interact with drugs that increase the sensitivity of the skin to sunlight, such as certain classes of antibiotics (tetracyclines and fluoroquinolones), antifungal medications, chemotherapeutic agents, retinoids, NSAIDs, and diuretics (dermnet.org).

Sources and dosing:

Photobiomodulation is available through specialized clinics and via home-use devices.
While various photomodulation devices have been cleared by the FDA, photobiomodulation has not been clinically validated in large, controlled clinical trials for any health condition. The studies conducted to date tend to be small, and the stimulation devices and parameters vary substantially across studies, such that we lack strong evidence about 'the best' devices and/or stimulation parameters for a given condition. For conditions that respond to photobiomodulation, benefits are often observed from a variety of stimulation parameters, suggesting that the parameters do not need to be optimal to have a beneficial effect. The robustness and durability of the effects may, however, be impacted by the stimulation parameters. Another key question that remains unclear is the duration of sessions needed for a response. The results from many studies suggest that a minimum number may be required, and that continued sessions may be needed for maintenance of efficacy. This will likely vary depending on both the condition and the stimulation parameters. It is also unclear if there is an upper limit to the therapeutic responses, such that additional sessions may allow for maintenance but do not provide further benefit.

Currently, the best course of action may be to look for devices/ clinic procedures, which use stimulation parameters that experts suggest are within the range that show that capacity to modulate cellular biological processes (e.g. mitochondrial activity) in preclinical studies. This generally translates to a target fluence level of 1 to 10 J/cm^2 [3]. However, unless the target is the skin, this is not necessarily the same as the fluence level used at the target tissue. The thickness of the intervening tissue needs to be

taken into account, as well as the optical scattering properties of the overlying. For deeper tissues, this calculation is not trivial, and highlights that this type of intervention likely has greater utility for more superficial targets.

Power densities of 1 to 100 mW/cm^2 are generally recommended, though brain studies often need higher levels (around 75 to 250 mW/cm^2) [81]. Relative to continuous light, pulsed light tends to allow for deeper penetration with less power [2]. Since fluence is a product of power density and time, lower powered devices generally need lower stimulation periods to have a desired effect.

Additional considerations may be needed for stimulation devices targeting the brain. Some research groups have determined that fluences of 0.9 to 15 J/cm^2 at the level of brain tissue can have direct cellular effects within brain cells [2]. Based on experimental studies, around 2% of light from near-infrared light (e.g. 810 nm, 980 nm, 1064 nm) can penetrate into the first few millimeters of brain tissue, with the caveat that the power source needs to be sufficiently high enough to allow the light to penetrate over a centimeter of overlying skin and bone tissue [2]. Some research suggests that low level power sources, such as 20 mW LEDs, may be insufficient to reach into the brain, though there are discrepancies across studies [2]. Another important consideration is diode placement, since areas of the head covered by hair are unlikely to allow a meaningful amount of light to penetrate into deeper tissues [2].

Specialized clinics may provide access to PBM using high powered lasers which would not be available through home devices.

Research underway:

According to ClinicalTrials.gov, there are currently approximately 150 active clinical trials testing photobiomodulation therapy. These largely fall into several key categories.

Cognitive/brain function-related: Epilepsy, ADHD, autism, Down syndrome, Alzheimer's disease, MCI, cognition/brain function, concussion recovery, traumatic brain injury.
Cancer/treatment side effect-related: Chemotherapy-induced peripheral neuropathy, chemobrain, mucositis, hand-foot syndrome, chemotherapy-induced alopecia, cancer-related lymphedema, lymphoma, radiation-induced dermatitis.
Muscle/Joint pain/function-related: Temporomandibular joint disorders, knee osteoarthritis, muscle spasticity.
Mood disorders: Depression, anxiety disorders.

Healing-related: Bone fracture recovery, healing of ulcers.
Pain-related: Postoperative pain, orthodontal procedures, tooth pain, pelvic health, chronic knee pain, back pain.
Inflammation-related: Periodontitis, heart failure, dry-eye syndrome, hypertension, sickle-cell disease
Sensory loss-related: Anosmia, age-related macular degeneration.

Search terms:
Pubmed, Google: Photobiomodulation, transcranial photbiomodulation, low level laser therapy

- Alzheimer's disease, cognition, Parkinson's disease, neurodenerative disease, dementia, clinical trial, aging, healing, pain, neuorpathy, meta-analyisis, safety, stimulation parmeters

Websites visited for Photobiomodulation:

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