PERIPHERAL ARTERIAL DISEASE (PAD) is typically caused by progressive narrowing of the arteries in the lower extremities. This condition affects 5–12 million Americans (43, 75), and the hallmark symptom is exertional pain in the buttocks, thigh or calf that promptly resolves with rest, termed “intermittent claudication.” However, only 10–15% of patients have classic claudication symptoms. In part because of the varied and often nonspecific presentation of symptoms, PAD remains poorly understood by the public, it is under-diagnosed in the primary care setting, and patients rarely receive optimal treatment (43, 44). Because PAD is an atherosclerotic disease, it is not surprising that patients with PAD are at high risk for myocardial infarction, stroke, and all-cause mortality (20). Indeed, patients with a history of PAD have the same relative risk of cardiovascular death as patients with coronary or cerebrovascular disease (19, 33). To further emphasize this fact, patients with PAD are three times more likely to die over the next 10 years compared with healthy individuals (20). From a physiological standpoint, the diagnosis and treatment of PAD involves fundamentals of fluid dynamics, metabolism, autonomic control of blood pressure, and the integration of multiple body systems. In this report, we describe 1) the pathogenesis of atherosclerosis (Fig. 1); 2) the clinical presentation and diagnosis of PAD; 3) the physiological consequences of chronic limb ischemia (Table 1); and 4) the physiological basis of current and future therapies in PAD (Table 2 and Fig. 2).

PATHOGENESIS OF ATHEROSCLEROSIS

As recently stated (30), “Atherosclerosis is a chronic immunoinflammatory, fibroproliferative disease of large and medium-sized arteries fueled by lipid.” This all-encompassing definition involves physiological processes at the cellular and molecular levels. The basic steps in the formation of an intraluminal thrombus (e.g., in the leg of a PAD patient) are as follows. First, LDL cholesterol from the blood passes through the dysfunctional endothelial cells and enters the intima media where it is oxidized. Second, monocytes sense the local inflammation and migrate to the arterial wall. Third, monocytes engulf the oxidized LDL and become foam cells, which appear histologically as a fatty streak. When the foam cells die, they release their lipid content, creating a lipid core. Fourth, smooth muscle cells proliferate and form a fibrous cap over the lipid core. Fifth, as more LDL accumulates, the external elastic membrane will expand (i.e., outward remodeling) in an effort to maintain blood flow. Eventually, the vessel will not be able to compensate and the plaque will protrude into the lumen, thereby raising both resistance and stiffness. Over time, subclinical plaque rupture followed by normal healing is a major physiological mechanism by which thrombi increase in size and reduce perfusion to distal targets.

It is important to emphasize that environmental irritants (e.g., cigarette smoking) and cardiometabolic risk factors (i.e., hypertension, hyperlipidemia, diabetes, and physical inactivity) as well as genetic factors contribute to the initial stages of this process (Fig. 1). It should also be noted that there is considerable overlap and redundancy between the stages. For instance, oxidized LDL reduces the formation of nitric oxide and potentiates the formation of endothelin-1 (78). The circulating hormone angiotensin II promotes atherosclerosis by forming reactive oxygen species (ROS) in macrophages, endothelial cells, and vascular smooth muscle cells. These ROS contribute to further oxidation of LDL cholesterol. Taken together, a variety of cytokines, growth factors, hormones, and adhesion molecules participate in the formation of an intraluminal thrombus. Why this process manifests itself in the lower extremity of PAD patients is not entirely clear.

CLINICAL PRESENTATION AND DIAGNOSIS OF PAD

A patient with suspected PAD will undergo measurement of the ankle-brachial index (ABI) at rest. Because perfusion to the
lower extremity is reduced in PAD, the ankle blood pressure will be lower than the brachial blood pressure; lower ABIs (i.e., more severe disease) correlate with mortality (20, 63). It is interesting that in the current high-tech state of medicine, the diagnosis of PAD is largely based on straightforward integrative physiology techniques relating blood pressure and blood flow. Prior large-scale studies have advocated that anyone ≥50 yr who is a smoker or diabetic and all people ≥70 yr receive ABI measurements (1). Postexercise ABI measurements may provide additional sensitivity (1). The qualitative Fontaine stages (I = asymptomatic, II = claudication, III = ischemic rest pain, IV = tissue loss or gangrene) and Rutherford stages (0 = asymptomatic, 1 = mild claudication, 2 = moderate claudication, 3 = severe claudication, 4 = ischemic rest pain, 5 = minor tissue loss, 6 = ulceration or gangrene) are used to grade severity of limb ischemia (48, 64). In addition to symptoms of leg pain, PAD patients with advanced disease may also present with skin atrophy, loss of hair, coldness, and nonpalpable pulses.

Table 1. Physiological consequences of chronic limb ischemia

<table>
<thead>
<tr>
<th>Physiological Consequences</th>
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<tbody>
<tr>
<td>Already Determined</td>
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<tr>
<td>Number and size of type 1 muscle fibers</td>
</tr>
<tr>
<td>Capillary density in leg muscle</td>
</tr>
<tr>
<td>Muscle and blood levels of acylcarnitines</td>
</tr>
<tr>
<td>Muscle lactate accumulation during exercise</td>
</tr>
<tr>
<td>Maximal oxygen uptake</td>
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<tr>
<td>Endothelial function of limb blood vessels</td>
</tr>
<tr>
<td>Systemic markers of inflammation</td>
</tr>
<tr>
<td>Systemic markers of coagulation</td>
</tr>
<tr>
<td>Rise in arterial blood pressure during exercise</td>
</tr>
<tr>
<td>Possible Associations Not Yet Determined</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Possible Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. LDL is oxidized</td>
</tr>
<tr>
<td>2. Monocytes migrate to arterial wall</td>
</tr>
<tr>
<td>3. Foam cell formation</td>
</tr>
<tr>
<td>4. Smooth muscle cells proliferate and form fibrous cap</td>
</tr>
<tr>
<td>5. Outward remodeling</td>
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Healthy Artery

Artery with PAD

PHYSIOLOGICAL CONSEQUENCES OF CHRONIC LIMB ISCHEMIA

Metabolism in ischemic muscle. PAD is not solely a disease of circulatory insufficiency. Because of the chronic low-flow state, PAD patients have metabolic dysfunction within skeletal muscle that makes them less able to utilize the oxygen that is delivered. A series of studies were conducted demonstrating that PAD patients accumulate acylcarnitines in both the plasma and muscle during short duration exercise (5, 37). This indicates that substrates are not effectively oxidized in PAD and suggests that distal flow limitation alters oxygen utilization. In fact, resting levels of acylcarnitine inversely correlate with claudication-limited peak aerobic capacity (V\textsubscript{O2 max}) (41). Relative to control subjects, patients with PAD also have fewer type I fibers, accumulate lactate at lower exercise intensities, have reductions in some electron transport chain enzymes, and have impaired oxygen uptake kinetics (5, 6). As noted in Table 2, exercise training can restore many of these impairments. On a physiological level, it is interesting that PAD patients have increased mitochondrial content in skeletal muscle as well as increased mitochondrial enzyme activity (39). Previous investigators have hypothesized that these adaptations might improve oxygen utilization under low-flow conditions (5).

The physiological differences between acute and chronic reductions in peripheral blood flow (i.e., ischemia) should be

Table 2. Benefits of exercise training in humans with PAD

<table>
<thead>
<tr>
<th>Benefits</th>
<th>References</th>
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<tbody>
<tr>
<td><strong>Functional Benefits</strong></td>
<td></td>
</tr>
<tr>
<td>Improved maximal walking distance</td>
<td>31, 38–40, 61, 70</td>
</tr>
<tr>
<td>Improved pain free walking distance</td>
<td>31, 38–40</td>
</tr>
<tr>
<td>Increased quality of life</td>
<td>31, 71</td>
</tr>
<tr>
<td>Increased free-living physical activity</td>
<td>61, 70, 71</td>
</tr>
<tr>
<td><strong>Physiological Benefits</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased systemic inflammation</td>
<td>80, 84</td>
</tr>
<tr>
<td>Increased endothelial function</td>
<td>8, 57</td>
</tr>
<tr>
<td>Increased skeletal muscle oxidative capacity</td>
<td>28, 38, 39</td>
</tr>
<tr>
<td>Increased maximal oxygen uptake</td>
<td>28, 31, 38–40, 70</td>
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</table>

PAD, peripheral artery disease.
noted. Compared with acute ischemia via cuff occlusion or intra-arterial balloon inflation, PAD is characterized by chronic limb ischemia due to atherosclerosis as well as age-related impairments in vascular compliance. Thus an impaired ABI is due to the net effects of structural/mechanical changes within the arterial wall, functional impairments in compensatory vasodilation, and physical blockage of flow by atherosclerotic plaque (typically observed in large conduit arteries). Fundamentally, ischemia (and also hypoxemia) impairs O2 delivery to skeletal muscle, and the local vasculature can dilate in an attempt to increase blood flow and O2 availability. This classic “supply and demand” balance is well established in both health and disease and is a key concept of physiology (27).

Using an intra-arterial balloon catheter to impede blood flow to the working forearm muscle in healthy subjects, Casey and Joyner (12, 14) recently demonstrated that acute hypoperfusion of the forearm leads to a compensatory vasodilation (i.e., to balance the acute impairment in O2 delivery) at rest and during low-intensity exercise. Indeed, the magnitude of flow restoration correlated to the reduction in downstream vascular resistance (13) and nitric oxide and adenosine both were involved (12). The arterial balloon catheter model of Casey and Joyner is an advanced experimental technique that allows researchers to determine cause-and-effect mechanisms of acute limb ischemia beyond the use of external cuff compression. However, this technique is invasive and does not study atherosclerotic ischemia per se, but rather ischemia due to mechanical reductions in limb blood flow. Whether PAD patients are in a chronic state of hypoperfusion that leads to local reduction in vascular resistance (i.e., distal to a stenosis) is plausible but needs to be experimentally tested.

**Endothelial function and blood markers of vascular health.**

The endothelium is a monolayer of cells within blood vessels that participates in hemostasis, inflammation, and angiogenesis. Importantly, endothelial cells produce a myriad of factors that can increase or decrease vasomotor tone (85). Endothelial function can be experimentally tested in the limb and coronary arteries using a variety of invasive and noninvasive approaches (79). Epidemiological studies suggest that PAD patients have severely compromised endothelial function in the limbs, and this is likely due to the combined effects of oxidative stress, inflammation, elevated serum lipids, and impaired ability of endothelial cells to produce nitric oxide (9, 10). Indeed, levels of fibrinogen and C-reactive protein are elevated in PAD (9, 50, 67). Additionally, Pellegrino et al. (66) demonstrated that impairments in peripheral vascular endothelial function in PAD patients (brachial artery flow-mediated dilation) correlate to coronary flow reserve (i.e., a measure of coronary vasodilator capacity). This linkage is important to understand because patients with PAD have a high incidence of coronary disease (32).
HDL cholesterol is typically lower and LDL cholesterol and triglycerides are higher in PAD patients relative to healthy controls. Plasma-antiplasmin complex, a hemostatic activation marker, is elevated in PAD and may be able to identify patients at a higher risk for future myocardial infarction (21, 67). Cigarette smoking clearly enhances the progression of atherosclerosis (52). The renin-angiotensin-aldosterone system in PAD patients has not been comprehensively studied, but it is known that ACE inhibitors slow the progression of atherosclerosis and may favorably benefit functional capacity (17). Taken together, several pathophysiological processes are evident in PAD that reflect systemic atherosclerosis in addition to local reductions in blood flow.

Autonomic control of blood pressure and blood flow. The sympathetic nervous system serves as the principal integrated controller of myocardial function, regional distribution of blood flow, and blood pressure. Many cardiovascular disease states are associated with heightened sympathetic tone (11, 29). Specifically, preclinical and clinical studies in hypertension, heart failure, obstructive sleep apnea, and renal disease provided evidence that basal sympathetic activity as determined by heart rate variability, circulating levels of the sympathetic neurotransmitter norepinephrine, and directly measured sympathetic vasoconstrictor nerve activity (via microneurography) is increased and predicts cardiovascular risk (11, 29). A direct consequence of enhanced sympathetic activity is increased vasoconstrictor tone in the target organ(s), which decreases regional blood flow unless it is counterbalanced by a commensurate increase in blood pressure (perfusion pressure). Furthermore, increased sympathetic tone may contribute to endothelial dysfunction (42), a hallmark in the development of atherosclerotic disease. However, it is important to appreciate that under physiologic conditions, sympathetic activity to different target tissues (skeletal muscle, kidneys, coronary arteries, etc.) may be highly variable, and some of these target territories are very difficult to study in humans (29).

An understanding of the specific role of sympathetic neural control and dysregulation in PAD is very limited. Most patients with PAD suffer from comorbid conditions such as hypertension, diabetes mellitus, and renal disease, and many are cigarette smokers, conditions that by themselves are known to be associated with sympathetic activation and vascular dysfunction (15, 29, 34, 62). Therefore, the pattern of sympathetic neural regulation in PAD is likely the result of the integrated effects of reflex interactions, altered central integration, and vascular dysfunction and remodeling. To what extent sympathetic overactivity and dysregulation are cause or consequence of the underlying disease process, by what mechanism the sympathetic nervous system is activated and modulated, whether it directly contributes to disease progression, and how it exerts its potential adverse effects on the cardiovascular system in humans are topics of continued debate. One postulated mechanism of sympathetic activation involves enhanced central expression of angiotensin II and renin-angiotensin-aldosterone system (RAAS) activity, promoting generation of reactive oxygen species and inflammation that result in impaired baroreflex restraint and heightened peripheral chemoreflex sensitivity (26, 65, 68, 86, 88). The contribution of renal sympathetic nerves to this process in humans is an area of active investigation (74). In another model of sympathetic activation produced by intermittent hypoxia (68), downstream effects of the generation of the transcription factor hypoxia-inducible-factor (HIF)-1α, including oxidative stress, appear to be crucial (76). This model is highly relevant to hypertension in general and to the effects of smoking.

PAD patients have an augmented blood pressure response to dynamic exercise (2, 3, 55). Our laboratory recently demonstrated that this was due in part to an augmented muscle mechanoreflex (relative to healthy controls) and that oxidative stress may be involved (60). Recent studies provide evidence that the muscle metaboreflex is also augmented in a rodent model of PAD (82, 83, 87). As recently reviewed by Li and Xing (54), alterations in metabolically sensitive muscle afferent receptors (transient receptor potential vanilloid type 1, purinergic P2X, acid sensing ion channel) appear to underlie the augmented blood pressure response to muscle contraction in this model. The augmented pressor response to exercise in PAD may be a normal compensatory response to enhance skeletal muscle blood flow, but high afterload may damage the brain and heart over time. Prospective studies relating acute exercise adaptations to long-term medical outcomes are needed. Because dynamic exercise is the primary stimulus that provokes symptoms in PAD and because patients with more severe disease have larger pressor responses to exercise (60), we believe understanding this process is of paramount physiological and medical importance. Future work in PAD patients who also have diabetes may clarify how an augmented pressor response to exercise influences limb function.

In addition to the sympathetic nervous system, vagal activity, typically inversely related to sympathetic activity, may also play a role. Vagal activity can exert important anti-inflammatory effects, thus potentially inhibiting vascular inflammation that underlies systemic atherosclerosis (81). Conversely, in a hypertensive rodent model, sympathetic activation has been shown to promote cardiac fibrosis (cardiac remodeling) via effects on monocytes (53). Whether reduced sympathetic activity or enhanced vagal activity would translate into anti-inflammatory effects on blood vessels in humans with PAD is unknown.

PHYSIOLOGICAL BASIS OF CURRENT AND FUTURE THERAPIES IN PAD

Treatment for patients with PAD is aimed at improving maximal walking distance and functional capacity as well as reducing cardiovascular disease risk. Previous publications have outlined the medical, surgical, and lifestyle management of this progressive disease (36, 64). The following section will focus on the physiological mechanisms by which the following treatments are effective: 1) medical therapy; 2) surgical intervention; 3) exercise training; and 4) mechanical therapy.

Medical therapy. Drug treatment with statins and antiplatelet agents is necessary for the secondary prevention of coronary and cerebrovascular disease in PAD patients. Because of the prevalence of comorbid conditions, smoking cessation, blood glucose management, and treatment of hypertension and obesity is also required (36, 64). Medical management is aimed at symptom relief and slowing progression of atherosclerotic disease. Although there have been a number of drugs evaluated for use in patients with claudication, efficacy is only noted for cilostazol and antiplatelet agents (16, 72). Cilostazol is a phosphodiesterase inhibitor that suppresses platelet aggrega-
tion; it is also a direct vasodilator. Patients can note improvement in maximal and pain-free walking distance in as short as 4 wk. Other phosphodiesterase inhibitors have been noted to increase mortality in patients with advanced heart failure, thus cilostazol is contraindicated in patients with any level of heart failure (36). Taken together, these above medications are physiologically effective if they improve blood flow to the limb, prevent lipid accumulation and oxidation, and prevent coagulation (i.e., preventing further progression of atherosclerosis). However, epidemiological evidence suggests that many patients do not receive symptom relief with medical therapy alone; the physiological rationale is likely because drugs are not able to enhance limb blood flow to the levels observed with other therapies (listed below).

**Surgical intervention.** Restoration of limb blood flow can be achieved through angioplasty (with or without the addition ofatherectomy), stenting, and lower extremity bypass. Percutaneous management has the advantage of being less invasive, avoiding infection and incision and generally being performed as an outpatient. When conservative measures fail and claudication becomes lifestyle limiting, angiography with intention to treat becomes a logical next step. Femoral arterial access is often utilized with 5–7 Fr. sheaths typical for intervention. If percutaneous treatment is deemed not possible by the physician, proximal and distal targets will be identified on angiography for lower extremity bypass planning. Autogenous conduits using great saphenous vein is preferred over prosthetic graft that carries a higher risk of infection, thrombosis, and decreased limb salvage compared with vein. Hybrid procedures exist that can combine these two modalities—endovascular and open vascular surgery—under one anesthetic. Hybrid operating rooms are becoming increasingly common and offer many advantages for the patient, including the ability often to make the entire procedure less invasive, as well as combining two procedures into one. On a physiological level, it is not surprising that surgically removing an obstruction to flow improves symptoms in PAD. How these standard of care procedures influence other body systems (e.g., muscle metabolism, autonomic nervous system, inflammatory processes) is an area for future investigation.

**Exercise training.** The benefits of exercise training in PAD are well established and are outlined in Table 2. As noted by Hamburg and Balady (35) in a recent review, the current recommendations include treadmill walking 3–5 days/wk up to the point of mild to moderate pain (35). Once pain is experienced, subjects are encouraged to rest and repeat the bout of exercise when symptoms resolve. In animals with experimentally induced limb ischemia, exercise training leads to angiogenesis and collateralization (35); whether this occurs in humans is unclear. Resistance training, arm ergometry, and modified cross country skiing have also shown positive benefits (35). It is important to emphasize that supervised programs are more effective than home-based programs (70). However, unlike cardiac rehabilitation programs, health insurance typically does not cover exercise for PAD patients (35). Whether exercise training is equal to or more effective than surgical intervention has been debated (18, 56, 61). Nevertheless, there is sufficient evidence that whole body dynamic exercise provides primary and secondary benefits in PAD. On a physiological level, these benefits are due to complex interactions between oxygen delivery and oxygen extraction in skeletal muscle.

**Mechanical therapy.** Patients with moderate to advanced PAD (Fontaine II-IV) are often unwilling or unable to exercise at the required intensity needed to achieve cardiovascular and functional benefit. For this reason, several mechanical devices have been developed that act on the arterial and/or venous systems. The most commonly studied therapy is intermittent pneumatic foot and calf compression (IPCC). Using the physiological principles set for by Le Dentu in 1867 (51) IPCC facilitates the venous emptying of the foot veins into the more proximal leg veins. Inflation pressures ranging from 85 to 180 mmHg are delivered to the foot and/or calf for 2–4 s, and this compression is followed by 16–20 s of rest (deflation). This paradigm is recommended for 2–6 h/day and allows for sustained flow while the veins refill (23–25, 46). Patients with both claudication and critical limb ischemia have experienced improvements in walking distance, improved quality of life, improved ABI, reduced leg pain, and reduced incidence of amputation (22, 45, 59). This is important for critical limb ischemia patients because they would not normally be encouraged to participate in a dynamic exercise program. The mechanisms by which this occurs have been widely speculated (23, 24, 46, 49, 69) but until recently have not been directly tested: 1) increased arteriovenous pressure gradient; 2) production of vasodilator substances due to increased shear stress; and 3) inhibition of the venoarteriolar reflex (which would normally act to impair blood flow when the limb is dependent). Recent studies in rodents investigated the effect of intermittent pneumatic leg compression on skeletal muscle performance, exercise tolerance, blood flow, oxidative capacity, and capillary contacts (73). The investigators found that 2 wk of daily treatment enhanced exercise performance and increased blood flow to the plantaris muscle compared with sham-operated animals. Another study from the same group found that intermittent compression transiently altered the expression of some (e.g., CYR61 and CTGF), but not all (e.g., VEGF), genes in human subjects (77). On a physiological level, these cited studies importantly help clarify the mechanisms by which intermittent compression provides clinical benefits.

Two other mechanical therapies include enhanced external counterpulsation (EECP) and remote ischemic preconditioning (RIPC). EECP is an effective therapy for the treatment of refractory angina and utilizes principles of hemodynamics in relation to each cardiac cycle (58). The patient is situated in the semi-supine posture with cuffs on the lower legs, thighs, and buttocks. During early diastole, the cuffs sequentially and rapidly inflate to suprasystolic pressure (distal to proximal); during end diastole the cuffs simultaneously deflate. This occurs for 60 min, 5 times/wk for 7 wk. By unloading the vasculature during systole and augmenting diastole, cardiac output is increased. Additional benefits are long lasting and include reduced proinflammatory markers, improved endothelial function, and reduced arterial stiffness (58). A diagnosis of PAD has been considered a relative contraindication for EECP but recent studies have indicated its safety (7). Many of the cardiac patients who benefit from EECP likely have systemic atherosclerotic disease (i.e., beyond just refractory angina). The concept that EECP might improve both limb and cardiac function in PAD needs to be prospectively tested. We should emphasize that the use of EECP in PAD patients must be performed in a medically supervised facility, and discussion...
should progress to standardize prescreening tests (e.g., imaging, blood panels) to minimize risk to the patient.

Similar to EECP, RIPC has gained attention in recent years, albeit in patients with coronary disease, not necessarily PAD (47). The fact that acute limb ischemia may protect against future limb or coronary ischemia is an attractive notion for patients who are unable to undergo exercise training or who do not respond to medical therapy. By making an arm or leg ischemic for 5 min, a cascade of hemodynamic and biochemical events occur that appear to offer both short-term and long-term systemic cardioprotection (4). Many of these studies have been performed in nonhuman models, but recent evidence suggests that 3–5 cycles of 5 min upper arm ischemia followed by reperfusion reduces infarction size and reduces troponin levels in cardiac patients (47). Whether a similar effect is seen in PAD patients remains to be directly tested. Compared with IPPC, EECP and RIPC modalities have not been comprehensively investigated yet, but we believe there is a physiological rationale for why they could/should be effective in PAD. RIPC is the shortest duration stimulus and also the least expensive, but the magnitude and duration of clinical benefits is currently unknown.

SUMMARY AND FUTURE DIRECTIONS

PAD is a common and progressive atherosclerotic disease that is closely linked with cardiac and cerebrovascular mortality. Its hallmark symptom, intermittent claudication, is provoked by moderate to vigorous leg exercise, but less than 25% of patients with PAD experience claudication, which makes the disease challenging to diagnose and treat (43, 75). Despite recent efforts, PAD is underdiagnosed in the primary care setting (47). Whether a similar effect is seen in PAD patients remains to be directly tested. Compared with IPPC, EECP and RIPC modalities have not been comprehensively investigated yet, but we believe there is a physiological rationale for why they could/should be effective in PAD. RIPC is the shortest duration stimulus and also the least expensive, but the magnitude and duration of clinical benefits is currently unknown.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


Physiology in Medicine


