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Diabetic Foot Disease in People with Advanced Nephropathy and Those on Renal Dialysis

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Abstract Among the spectrum of risk for diabetic foot disease conferred by chronic kidney disease (CKD), end-stage renal disease (ESRD) has emerged as a novel independent risk factor. Apart from the classical triad of neuropathy, infection, and peripheral arterial disease that operate in these individuals, the risk is further compounded by inadequate foot self-care by patients and by dialysis centers not providing onsite foot care, as medical priorities are diverted to the dialysis itself. Consequently, the burden of diabetic foot disease has increased in the CKD and ESRD population as exemplified by high ulceration, amputation, and foot-related mortality rates. Current guidelines on foot care in diabetes should recognize advanced CKD and ESRD/dialysis as a separate risk factor for foot disease to alert professionals and highlight the opportunity for prevention. Recent studies have demonstrated improved foot outcomes when chiropody programs are instituted within dialysis units.

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Clinical Trial Acronyms

ARIC	Atherosclerosis Risk in Communities
DOPPS	Dialysis Outcomes and Practice Patterns Study
HERS	Heart and Estrogen/Progestin Replacement Study.

Introduction

Foot ulceration is a common complication affecting up to 25% of patients with diabetes during their lifetime [1]. The direct costs to both the individual and the health care system associated with diabetic foot ulceration are high [2, 3], and these costs are doubled when foot ulceration results in an amputation [4]. The indirect costs are difficult to measure but would only magnify an already high direct cost [5].

Diabetes is the most common cause of end-stage renal disease (ESRD) in the Western world, responsible for about 20% to 45% of incident renal replacement therapy [6, 7]. ESRD invariably increases the risk of diabetic foot ulceration and amputation [8]. Therefore, the progression of diabetic nephropathy to more advanced renal failure and ultimately to dialysis treatment may be associated with an ominous rise in the burden of foot ulceration, and amputation with associated morbidity and mortality. Not surprisingly, there has been a renewed interest in understanding the association between diabetic foot complications and advanced renal impairment or ESRD, as illustrated by recent studies [9•, 10••, 11, 12••]. The surge in literature mandates a careful appraisal of the available data and the evidence base, to inform appropriate management

and/or prevention of diabetic foot disease, as well as to identify gaps in the literature that require further research. This review aims to revisit the clinical significance of diabetic foot disease in chronic kidney disease (CKD) including ESRD (dialysis) and to suggest strategies and opportunities for prevention.

The "Trilogy" of Risk Factors for Diabetic Foot Disease in Individuals with Advanced CKD and ESRD

The pathway to foot ulceration implicates various component causal factors that act in concert and result in a sufficient cause that leads to a breakdown in the skin epithelium and to chronic ulceration [13]. People with diabetes and those with advanced CKD or ESRD share three pivotal risk factors whose interaction undoubtedly increases their risk for developing foot ulceration and amputation: neuropathy, peripheral arterial disease (PAD), and increased susceptibility to infection with impaired wound healing. The deleterious impact on foot complications conferred by the coexistence of these three factors in people with diabetes and ESRD justifies the coinage of "trilogy of risk factors." As these factors have been extensively studied and characterized among people with diabetes, the ensuing sections will focus on their occurrence in CKD/ESRD and their mechanistic association with diabetic foot disease.

Neuropathy in Advanced CKD and ESRD

It is known that in people with diabetes, the severity of neuropathy increases with worsening renal impairment [14]. The occurrence of neuropathy in patients with ESRD was first suspected by Charcot in 1880. Since then, uremic neuropathy has been identified as a specific form of neuropathy occurring in patients with ESRD when the estimated glomerular filtration rate falls below 12 mL/min (< 25 mL/min in uremic myopathy), due essentially to the accumulation of dialyzable neurotoxins. Uremic neuropathy can affect the central, peripheral, and the autonomic nervous systems. Involvement of the peripheral nervous system occurs as a polyneuropathy that is insidious in onset and is present in 60% to 100% of people on renal dialysis [15, 16]. Similar to chronic sensorimotor neuropathy seen in diabetes, uremic polyneuropathy is characterized by axonopathy initially involving large myelinated fibers [17] with a "dying-back" phenomenon. Clinically, it manifests with numbness, sensory loss, paresthesias, reduction in deep tendon reflexes, impaired vibration sense, muscle wasting, and weakness. The neuropathy is length-dependent, thus evolving in a glove and stocking pattern. A paradoxical heat sensation in the setting of hypoesthesia to cold has been described as a harbinger of uremic polyneuropathy [18]. The coexistence with diabetes means that features of diabetic neuropathy will overlap with uremic polyneuropathy in CKD/ESRD individuals. Whereas adequate chronic dialysis may improve autonomic (cardiac) neuropathy and myopathy, the impact on polyneuropathy is less well established [19–21].

Uremic myopathy with wasting of the interosseous muscles of the foot may result in an unbalanced muscle pull on tendons and joints, ultimately leading to foot deformity, high plantar pressures, and increased susceptibility to foot ulceration. Additionally, the hyperesthesia of uremic neuropathy may give a false sense of being able to perceive painful nociceptive stimuli—a sensory modality that is frequently lost in people with diabetes, thus leading to paradoxical painful/painless feet that are at high risk for neuropathic ulceration. Autonomic neuropathy and intradialysis hypotension can predispose to instability, falls, and trauma, thus leading to increased susceptibility to foot ulceration.

PAD in Advanced CKD and ESRD

The strong association between PAD and CKD has recently become more apparent and pronounced. In a large community-based, 13-year follow-up of patients in the ARIC study, the incidence rate of PAD was found to increase with progressive severity of baseline CKD [22]. The incidence rates per 1,000 person-years were 4.7, 4.9, and 8.6 for stage 1, stage 2, and stages 3 or 4 CKD groups, respectively. These data confirmed earlier findings in a smaller cohort of postmenopausal women involved in the HERS study, showing that CKD is a predictor of future PAD events [23]. Therefore, CKD can be seen as a continuum of risk for PAD; ESRD or dialysis being at highest risk. In the DOPPS study, the overall prevalence of PAD among adult hemodialysis patients was found to be 25% [24]. In the subgroup of hemodialysis patients who had diabetes, age and "vintage" (length of time since commencement of dialysis) were significantly associated with PAD. Other studies involving peritoneal dialysis patients [25] and patients with stage 4 or 5 CKD but not on dialysis [26] have reported correspondingly high prevalence of PAD of 19% and 15%, respectively.

These variations in the reported prevalence of PAD in the ESRD or dialysis population have been attributed, at least in part, to subclinical (asymptomatic) PAD that many studies fail to capture, thus underestimating the true prevalence of PAD [24, 25]. However, the suggestion that ankle brachial pressure index (ABPI) measurement may

identify subclinical PAD [25] can be easily challenged, particularly in the ESRD population in which vascular calcification is highly prevalent [27, 28]. The coexistence of ESRD and diabetes, especially in those with neuropathy, further complicates the interpretation of ABPIs as vascular calcification has been reported to occur in more than one third of these individuals [29, 30]. Based on these premises, we [9•, 31] and other authors [32] have recommended using a combination of criteria to identify PAD among people with diabetes, including those who are on dialysis. Such criteria should include, among others, an assessment of peripheral pulses, Doppler waveforms, ABPIs, and where possible toe blood pressures as simple noninvasive methods.

The high prevalence of PAD in dialysis patients with diabetes is due not only to their advanced diabetes disease, but also to an increase in vascular risk factors. Mechanistically, a plethora of risk factors for PAD have been described in dialysis patients, including conventional cardiovascular risk factors and dialysis-specific factors. Among hemodialysis patients, cardiovascular risk factors associated with PAD in cross-sectional studies include age, white race, male gender, diabetes disease itself, coronary artery disease, stroke, smoking, and left ventricular hypertrophy, but not predialysis blood pressure or raised serum cholesterol [33, 34]. For patients on peritoneal dialysis, one cross-sectional study from Taiwan showed that PAD was associated with age, diabetes mellitus, and pre-existing cardiovascular and/or cerebrovascular disease [25]. Dialysis-specific factors that have been implicated in the development of PAD include vintage and malnutrition [25, 33]. Furthermore, two studies have reported an intradialytic drop in microvascular blood flow or tissue oxygenation (transcutaneous oxygen tension) during hemodialysis sessions [35, 36], which is most marked among subjects with diabetes [36]. It is thought that huge fluid shifts (and the resultant hemodynamic changes) during dialysis are responsible for this dialysis-mediated tissue hypoperfusion and that this may worsen any underlying PAD and also lead to friable skin and impaired wound healing. Changes in tissue perfusion in patients on peritoneal dialysis have not been evaluated.

Susceptibility to Infection in ESRD

The presence of diabetes undoubtedly increases the immune vulnerability of ESRD patients to infection and a hyperglycemic milieu constitutes a veritable broth medium for microbial growth and infection. Infections remain the second (20%) cause of mortality after cardiovascular causes (50%) and are responsible for significant morbidity in these patients. Furthermore, uremia represents a state of immune deficit affecting virtually all aspects of the defense against infection [37]. These perturbations have been ascribed to a uremic milieu responsible for hyporeactive monocytes [38] and decreased bactericidal action of neutrophils [39]. A state of significant perturbation [40] in complement function and increased cytokine production (from reduced renal clearance and recurrent infections) has also been described in dialysis subjects [41]. Dialysis procedures, iron overload, and anemia of chronic renal disease can further exacerbate disorders in polymorphonuclear cell function.

Other Risk Factors for Diabetic Foot Disease in ESRD

In addition to the "trilogy" of risk factors explained above, it seems very likely that several other factors explain the link between dialysis therapy and foot ulceration. These factors include physical and psychological health, reduced mobility and manual dexterity, visual acuity, poor nutrition, low serum albumin, adequacy of dialysis, anemia, leg edema, and leg/foot support during dialysis. Leg edema stretches the skin making it friable, and also compromises microvascular blood flow. Anemia is highly prevalent in ESRD, resulting in reduced tissue oxygenation and impaired wound healing. A follow-up study of 71 diabetic patients on peritoneal dialysis found that those who had a foot complication (ulcer, gangrene, PAD, foot infection) were more likely to have low serum albumin and more likely to have received higher doses of erythropoietin [42], thus further underpinning the etiopathogenetic role of hypoalbuminemia and anemia in foot complications. Poor vision and reduced dexterity may impair an individual's ability to perform foot inspection or foot self-care. In a study of dialysis patients (42% of whom had diabetes), 25% had inadequate vision, 40% had inadequate dexterity, and 45% had inadequate flexibility to perform self-care [43]. In addition, lying on a dialysis couch for several hours three times a week could also contribute to the development of pressure ulcerations especially on insensate heels and toes that impinge on the edge of the bed.

Mechanistically, during wound healing hypoxia-inducible factor-1α transactivates the synthesis and release of vascular endothelial growth factor (VEGF), which helps maintain angiogenesis. This transactivation requires the cofactor p300, but is inhibited by iron. It is plausible that iron repletion commonly used in the ESRD population to optimize erythropoiesis may inadvertently impair wound healing in these individuals. Recent evidence suggests that iron depletion with deferoxamine in rats improves tissue oxygenation and facilitates wound healing by abrogating iron-mediated impairment of VEGF upregulation [44].

Psychosocial Aspects of Diabetic Foot Disease in ESRD

Nonadherence to foot self-care is an important risk factor for diabetic foot disease in the ESRD population [45]. It has been reported that dialysis patients being generally sicker are overwhelmed with the rather stringent requirements of dialysis (eg, attending three hemodialysis sessions per week) and tend to neglect other aspects of care, particularly foot care [46, 47]. They also have more depression and other psychosocial factors that may affect compliance or influence their ability to keep clinic visits [48]. Depression is the most common psychiatric disorder among patients with CKD and ESRD, and has been associated with increased morbidity and mortality [49]. A recent study on major depression in patients with diabetes and stage 5 CKD found that approximately one in five patients met the criteria for this important comorbidity, and the risk of death was increased threefold in those with major depression [50].

Progressive Renal Impairment as a Continuum of Risk for Diabetic Foot Disease

Risk factors for foot ulceration are present at all stages, including the earliest stages, of nephropathy [14, 51]; microalbuminuria, the hallmark of diabetic nephropathy, is known to be an independent risk factor for foot ulceration [52]. Recently, Margolis et al. [10••] showed that when compared to patients with an estimated glomerular filtration rate (eGFR) greater than 60 mL/min (stage 1 and CKD), the hazards of foot problems were increased approximately twofold for patients with stage 3 CKD and by threefold for patients with stage 4 or stage 5 CKD. Moreover, they found that the association between CKD and foot disease was not entirely related to PAD, contrary to widely held assertions. As a corollary to the Margolis report [10••], the risk for foot disease has also been shown to decrease with improvement in renal function. For instance, Wolf et al. [11] recently reported that for every 10-mL/min increase in eGFR, the odds for developing foot ulcers reduced by 30% in people with type 1 diabetes (odds ratio [OR], 0.696) and by 13% in people with type 2 diabetes (OR, 0.873). Based on these reports, it is logical to contend that the spectrum of diabetic nephropathy from microalbuminuria through ESRD/dialysis represents a continuum of risk for diabetic foot disease, the greatest risk occurring in patients with ESRD and on dialysis.

Renal Dialysis as an Emerging Novel Risk Factor for Diabetic Foot Disease

One of the first reports providing some insights that dialysis is a risk factor for foot complications was the observation reported by Hill et al. [53]. In this study, the authors performed a cross-sectional assessment of diabetic patients with and without ESRD, and found that ESRD was associated with a fourfold higher risk of diabetic foot complications. Later, McGrath and Curran [54] retrospectively reviewed 47 diabetic patients who had had an amputation, 86% (32 patients) of whom were Maoris and 30% (14 patients) who were on dialysis. Among those patients on dialysis, the median time between starting dialysis to having an amputation was 7 months (range, 2 weeks to 40 months). These findings were later supported by those of Morbach et al. [55] who examined a predominantly Caucasian population of 400 patients with diabetic foot ulcers, 14 (4%) of whom were on dialysis. Since then, a substantial body of literature on diabetic foot disease in dialysis patients has been accumulating. Game et al. [12••] performed a retrospective case series analysis of 90 patients with diabetes who started dialysis and showed that the cumulative incidence of foot ulceration and amputation increased prior to the initiation of dialysis and then was highest during the next 2 years. Because the increase in foot complications occurred just prior to dialysis, it remained unclear whether the main driver of foot complications was the advanced CKD in the study cohort or the dialysis treatment itself.

A prospective study of foot complications in persons with diabetes on dialysis is our recent transatlantic (Texas USA, Manchester UK) study involving over 400 patients [9•]. In this study, at baseline we showed that all diabetic patients on dialysis are at high risk for foot complications independent of ethnicity (with 95% of the study cohort classified as risk category 1 or higher), based on the classification of the International Working Group on the Diabetic Foot (IWGDF). In a subsequent study, we consecutively enrolled 137 diabetic patients on dialysis and compared their risk for foot ulceration to 189 consecutive predialysis patients (stage 4 or stage 5 CKD but not on dialysis) [56]. In multivariable logistic regression analysis, dialysis therapy was found to be independently associated with an increased risk for foot ulceration (OR, 4.2 [1.7–10]), even after including potential confounders (neuropathy, PAD, foot self-care measures, ethnicity) in the final model.

Ethnicity did not affect the association between dialysis and foot ulceration. This finding refuted previously reported ethnic disparities in the risk of foot complications in the general diabetes population, whereby ethnic minorities in the United Kingdom (Africans and Indo-Asians) appeared to be protected whereas in contrast, minorities in the United States (Hispanics and blacks) appeared to be at higher risk compared with whites. Judging from the odds ratios, the risk for foot ulceration associated with dialysis treatment was even higher than that associated with a past

history of ulceration. This was the first cross-sectional study to show an independent risk association between dialysis and foot ulcers. Classical and putative risk factors for foot ulceration were included in the multivariable analysis, but this did not attenuate the association between dialysis and foot ulceration. Therefore, in agreement with the Margolis et al. paper [10••], data from this study challenged the previously held belief that advanced disease (advanced neuropathy, PAD, poor metabolic control) was the key driver of foot complications in ESRD. We concluded that the dialysis treatment itself—and to some extent other comorbidities associated with it—constitutes a unique and novel foot ulceration risk. Therefore, we proposed that in the hierarchy of risk factors for foot ulceration proposed by the IWGDF classification and similar guidelines (eg, guidelines from the foot council of the American Diabetes Association, and the American Podiatric Medical Association), renal dialysis should be considered as a high risk status for diabetic foot complications, equal in importance to foot ulcer history or prior amputation. An analogy could be drawn between dialysis as a foot ulcer risk equivalent and the more established concept in cardiovascular medicine, in which diabetes is considered a coronary heart disease equivalent. This implies a paradigm shift from the traditional "high-risk factors" to "high-risk groups," an approach that arguably offers more promise and opportunities for prevention as discussed below. The high risk for diabetic foot ulceration associated with dialysis/ESRD is probably of a magnitude that any small ethnic variation becomes insignificant, making the collective ESRD population a high-risk group.

Outcome of Diabetic Foot Disease in Individuals with ESRD

Amputation rates are disquietingly high in people with diabetes and ESRD. Data from the Medicare population in the United States report nontraumatic amputation rates of 11.8 to 13.8/100 person-years in diabetic patients on dialysis, rates that are 10 times higher than in the overall diabetic population [8]. Similarly, the presence of diabetes—whether as the underlying cause of ERSD or as a pre-existing comorbidity—appears to be the strongest risk factor for lower limb amputations among hemodialysis subjects (hazard ratio, 6.4; CI, 3.4–12.0) [57]. The nefarious impact of amputation on quality of life and the associated costs to the individual and society cannot be overstressed. Furthermore, CKD is strongly associated with postoperative death after lower extremity amputation. Using data from the Veterans Administration, O'Hare et al. [58] reported 30-day postoperative amputation mortality of 9% in patients with moderate CKD, 15% in patients with severe CKD, and 16% in dialysis patients, compared to 6% in patients with normal or mildly reduced renal function.

Even after successful postamputation rehabilitation, mortality rates in amputees on dialysis are disproportionately high. One small study that included 14 diabetic patients on dialysis reported a 1-year mortality of 50% [54]. This compares to 33% 1-year mortality rates in diabetic patients after admission for heart failure. There is a dearth of data on long-term postamputation mortality in patients on dialysis. We recently analyzed data from a relatively large cohort of diabetic patients in Texas and observed that postamputation mortality rates increased with the severity of renal disease, with dialysis patients having the most dismal prognosis [59•]. One- and 5-year survival rates were 50.8% and 17.2%, respectively, in hemodialysis subjects, compared with 76.6% and 40.9% for individuals with chronic moderate-to-severe CKD (eGFR<60 mL/min), and 85.6% and 60.3% for those with mild or no CKD (eGFR> 60 mL/min). In addition, compared to individuals with no renal disease, survival analysis indicated that there was a 290% increase (OR, 3.9; CI, 3.07–5.0) in hazard ratios for death for subjects on dialysis and a 46.5% increase (OR, 1.465; CI, 1.213–1.77) for subjects with CKD. To put these data into perspective, 5-year mortality after myocardial infarction in patients with diabetes is 72% [60], and 5-year survival after ischemic stroke has been reported to be 59.5% [61].

It may well be that a different hierarchy of causes of mortality occurs in individuals on dialysis after undergoing an amputation, with infection/sepsis contributing as much as cardiovascular disease, the traditional cause of mortality in dialysis subjects. There is some circumstantial evidence to support this assertion; in a case-control study to determine mortality rates after diabetes-related amputation in African-Caribbean blacks, Hambleton et al. [62] found that the high mortality rates were due to sepsis (49% of cases) followed by cardiac disease (45%). Although this study was not performed primarily on dialysis subjects, it nevertheless highlighted the fact that vulnerability to sepsis augments mortality rates. This finding is of the utmost relevance when considering diabetic patients on dialysis, given their increased susceptibility to infection/sepsis.

Prevention of Diabetic Foot Disease in Individuals with ESRD

The burden of diabetic foot disease in patients on dialysis as exemplified by high morbidity, mortality, and costs makes any emphasis on the need for prevention and appropriate management obvious. The case for prevention is so compelling that it is hard to understand why foot care is not yet an integral part of most dialysis units worldwide.

We recently showed that prevention programs are not provided even to individuals at the highest risk for foot ulceration (dialysis, previous ulceration, or amputation). Several reports show a beneficial effect of instituting foot care or chiropody programs within dialysis centers. Lipscombe et al. [63] performed a retrospective analysis of diabetic patients on peritoneal dialysis at the university health network, in Toronto. They found that the percentage of patients with serious foot problems who had an amputation dropped from 50% (10/20) at baseline (no chiropody program) to 33% (7/21) in the period when a chiropodist provided assessment and education on foot care, and further down to 10% (2/21) when onsite foot care was introduced at the same center. From their regression analysis, they concluded that being seen by a chiropodist was protective from death or amputation (hazard ratio, 0.39 [0.05–0.73]; $P<0.01$). Another small study of 23 male patients with diabetes on hemodialysis also showed that a structured foot care education, foot assessment, and provision of special shoes, all led by a dialysis nurse, was associated with beneficial outcomes [64].

Nonetheless, the effectiveness of interventions to prevent foot complications has been established in the general diabetes population. Specialized diabetic foot programs have been reported to reduce the incidence of amputations by 50% [65–67]. The study by Foster et al. [65], which focused on renal transplant patients, showed that when structured foot care was instituted, ulcer healing times were improved to levels that were similar to the general diabetes population. Uccioli et al. [68] also demonstrated approximately 50% reduction in foot ulceration when therapeutic shoes were prescribed for patients with an ulcer history, compared with patients who selected their own shoes, and other studies have demonstrated a reduction in recurrent ulceration in patients receiving regular foot care [69].

Therefore, it appears that a good foot disease prevention package for patients on dialysis should be based on 1) a multidisciplinary approach involving a dedicated foot care team; 2) accessibility and proximity to foot care (ie, foot care within dialysis units); and 3) continuous ongoing education. Based on these premises, one can conceive a minimalistic model of foot care for dialysis patients (Table 1).

Conclusions

Diabetic foot complications are common in patients with renal impairment, with the risk of developing such complications highest in patients on dialysis. Over the past few years, renal dialysis has emerged as a novel independent risk factor for diabetic foot disease. This constitutes a remarkable burden associated with significant morbidity, mortality, cost, and implications for quality of life. A triad of risk factors for foot ulceration—neuropathy, PAD, and infection—must also be recognized in people with diabetes on renal dialysis, in addition to the independent impact of ESRD or dialysis. The opportunity for prevention could not be more obvious given that dialysis patients have multiple visits to the hospital, yet preventative foot care programs are lacking in most dialysis centers. Because diabetes is the most common cause of ESRD in the Western world, the coexistence of the two conditions constitutes a double whammy that threatens to jeopardize limb salvage attempts worldwide. It is imperative for professionals caring for people with diabetes to recognize this challenge and implement foot care programs for subjects with renal

Table 1 A minimalistic model of foot care for dialysis patients

Centered on a nurse, podiatrist, or suitably qualified health professional with a keen interest in diabetic foot disease
Ongoing support from a designated podiatrist/chiropodist, an orthotist or shoemaker, and a diabetes or renal physician, depending on available personnel
Routine and systematic assessment for neuropathy, PAD, callus, foot deformity, bed sores, pre-ulcerative lesions, ulcers and infection or gangrene in all patients, with the foot rendered completely bare (ie, no socks or shoes)
Routine examination of the heels and toes because these areas may suffer from pressure damage due to the insensate foot (from neuropathy) impinging on the edge of the bed
Prompt treatment of simple lesions during or immediately at the end of the dialysis sessions or clinic appointment
Treatment of infections with appropriate antibiotics
Immediate referral of cases of suspected PAD to the vascular team for confirmation and/or intervention
Timely referral to a podiatrist and/or shoemaker for patients needing offloading or bespoke footwear
Regular meetings between the team of nurse, podiatrist, shoemaker, physician, vascular surgeon, and other members to audit progress and set new service targets
Programmed patient education sessions should be organized individually or in groups
Augmented educational support through the use of foot care videos while patients are on dialysis machine (hemodialysis) or in the waiting room of renal outpatient departments (peritoneal dialysis)

PAD peripheral arterial disease.

impairment, particular those on dialysis. A multidisciplinary diabetic foot care program that is integrated within dialysis units and run by a dedicated cadre of staff is paramount to successfully reduce foot ulceration, save limbs, improve quality of life, and reduce mortality in diabetic patients with ESRD. However, data on the cost effectiveness of such prevention programs are sparse; thus, carefully designed clinical trials are urgently warranted.

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- •• Of major importance

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