A New Era with the Development of Cytokine-Based Therapy for Pruritus

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Pruritus is a common dermatological condition and negatively impacts QOL. Persistent pruritus and excessive scratching behavior can lead to the itch–scratch cycle that exacerbates inflammatory skin diseases. Conventional antipruritic drugs, such as antihistamines, corticosteroids, or anticonvulsants, are sometimes insufficient. Recently, however, molecularly targeted drugs, such as IL-31 or IL-4 receptor–targeting antibodies, have become available or are under clinical trials, dramatically changing the clinical situation. In fact, some of these drugs can improve pruritus without the need for topical steroids. Taken together, these observations point to the importance of cytokine-mediated pruritus, further understanding of which may guide improved therapies.

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INTRODUCTION

Pruritogen exposure to an individual's skin causes pruritus/itch—an urge to scratch the irritated area. Itch sensation is biologically important as a host defense mechanism. However, persistent pruritus and excessive scratching behavior cause a condition called the itch–scratch cycle, which can worsen inflammatory skin diseases. Pruritus is one of the most common complaints in dermatology, with more than one-third of dermatology patients suffering from this condition (Wong et al., 2017).

Chronic pruritus is clinically defined as pruritus that lasts at least six weeks, although most patients suffer from pruritus for much longer, ranging from months to years (Mack and Kim, 2018; Ständer et al., 2007; Wang and Kim, 2020). One study reported that 90% of patients with chronic inflammatory diseases experienced pruritus, and a relationship was noted between the intensity of pruritus and impaired sleep quality, work productivity, and mental health (Hawro et al., 2021). Unfortunately, conventional drug therapies, such as antihistamines, do not sufficiently control chronic pruritus. Indeed, recent advances have revealed that multiple independent factors (e.g., histamines, neuropeptides, and cytokines) are closely linked to induce pruritus under each chronic inflammatory condition (Wang and Kim, 2020). Therefore, understanding the mechanism of pruritus and establishing treatments based on this understanding are urgently needed.

CLINICAL BURDEN OF PRURITUS

The negative impact of chronic pruritus on QOL is shown to be just as debilitating as that in chronic pain (Kini et al., 2011). A cross-sectional study of 602 US adults with atopic dermatitis (AD) reported that pruritus was the most burdensome symptom (54.4%) and that severe itch scores, using the patient-oriented scoring AD-itch scale, were associated with poor mental health (Silverberg et al., 2018). Another cross-sectional study of 132 North American adults with chronic pruritus revealed that these patients exhibited significantly worse health performance compared with healthy controls, which was evaluated by a paper-based QOL survey that included the Health Utilities Index Mark 3 and dermatology-specific instruments, such as ItchyQoL, Dermatology Life Quality Index, and Skindex-29 (Whang et al., 2021b). Chronic pruritus is also closely linked to psychiatric conditions, as evidenced by a high prevalence of depression or suicidal ideation in patients with chronic pruritus (Hawro et al., 2021; Jafferany and Davari, 2019). Furthermore, itch sensation also impairs sleep quality (Hawro et al., 2021); a study of 126 patients with inflammatory skin diseases found that 69.8% of patients suffered from itch-related sleep disturbance (Chee et al., 2020). Another analysis found chronic pruritic dermatoses to be associated with increased nighttime awakenings (Patel et al., 2021).

In parallel, patients with chronic pruritus suffer from substantial economic burden. One study indicated the annual median total costs of chronic pruritus to be $1,067 per patient (Luk et al., 2020), whereas another study on patients with chronic pruritus in North America calculated the lifetime economic burden for individuals to be $274,921 and the societal burden to be approximately $88.81 billion (Whang et al., 2021b). Scratching behavior could result in skin breakdown and increased risk for infection, which yields direct medical costs, including consultations, referrals, laboratory tests, and prescription medication, arising from attendance at emergency departments and hospitalization (Kabashima and Irie, 2021; Whang et al., 2021a, 2019). Moreover, pruritus is associated with indirect costs, such as reduced work, poor school productivity, over-the-counter treatments, and time required to apply topical agents or other self-treatments (Luk et al., 2020).

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Abbreviations: 5-D, five-domain; AD, atopic dermatitis; DC, dendritic cell; EASI, Eczema Area and Severity Index; KC, keratinocyte; NRS, numerical rating scale; STAT, signal transducer activator of transcription; VAS, visual analog scale

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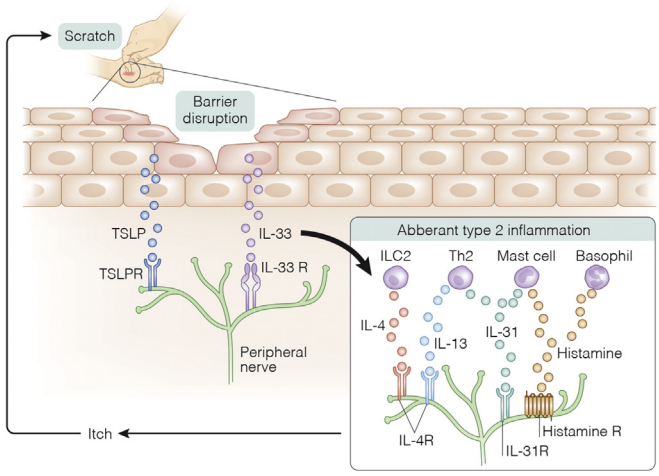

Figure 1. Inflammatory mediators involved in chronic pruritus in skin lesions of AD. Continuous itch-induced scratching behavior can damage the skin barrier, leading to the release of inflammatory mediators from damaged keratinocytes, such as TSLP or IL-33. These mediators act on skin-resident immune cells, such as mast cells and ILC2, to stimulate type 2 allergic inflammation and contribute to the development of further inflammation. Type 2 immune cells, including Th2 cells, ILC2, basophils, and mast cells, produce a variety of itch-inducing molecules, such as histamine and cytokines (IL-4, IL-13, and IL-31), which promote pruritus in AD skin lesions. AD, atopic dermatitis; ILC2, group 2 innate lymphoid cell; Th, T helper; TSLPR, TLSP receptor. *Illustration assistance provided by katierisvicari.com.*

CHRONIC PRURITUS IN AD

The role of the itch–scratch cycle in the pathogenesis of skin disorders is most exemplified in AD (Mack and Kim, 2018). AD is a chronic and relapsing inflammatory skin disorder characterized by skin barrier disruption and abnormal immune responses. Itch sensation is the major symptom in AD and is often uncontrollable, despite conventional medications. Moreover, impaired QOL in patients with AD is correlated with disease severity, increased pruritus, and sleep disturbance (Drucker et al., 2017).

Although the precise mechanism of chronic pruritus in patients with AD is not clear, it may be schematically explained by two aspects: skin barrier disruption and abnormal immune response (Figure 1). Underlying defects in the skin barrier caused by loss-of-function mutations in the epidermal barrier protein FLG in humans are well known to be associated with a heightened risk for developing AD (Palmer et al., 2006). However, other factors, such as decreased ceramide formation, disorganized tight junction, or increased serin proteases, could also contribute to the pathogenesis of AD (Tsakok et al., 2019; Yang et al., 2020). Meanwhile, continuous itch-induced scratching behavior itself can damage the skin barrier and provoke prolonged irritation, leading to the release of inflammatory mediators from damaged keratinocytes (KCs), such as TSLP and IL-33. These mediators, known as alarmins, act on skin-resident immune cells, such as dendritic cells (DCs), mast cells, and group 2 innate lymphoid cells, to stimulate type 2 allergic inflammation, where a variety of itch-inducing molecules, including histamine, neuropeptides, and cytokines including IL-4, IL-13, and IL-31, are produced and stimulate the peripheral nerves (Wang and Kim, 2020). Simultaneously, type 2 immune response in the skin can reduce the expression of FLG and the epidermal lipid formation in the lesional skin of AD, deteriorating skin barrier function and further promoting the release of proinflammatory mediators (Howell et al., 2009; Yang et al., 2020). This vicious cycle of inflammation-induced skin barrier impairment could contribute to prolonged pruritic sensation in patients with AD.

CYTOKINE-MEDIATED PRURITUS IN AD

Various therapeutic options have been used for pruritus in AD and other chronic pruritic skin disorders (e.g., prurigo nodularis, psoriasis). Although these treatments are effective to some extent, they generally do not achieve sufficient remission of pruritus. One reason is that, at least in AD, multiple independent factors may be involved in the development of chronic pruritus (Figure 1). Antihistamines, occasionally used as first-line drugs for pruritus, do not suppress pruritus caused by other mediators. Anticonvulsants and opioid modulators are primarily effective for pruritus in the central nervous system. Topical or oral steroids can be expected to reduce pruritus as a result of controlling skin inflammation.

However, the situation has changed dramatically in recent years because various molecularly targeted drugs have been used to treat moderate-to-severe AD (Figure 2) (Yang et al., 2021). These drugs not only improve skin rashes but are also effective in eliminating pruritus. Some of these drugs even improve pruritus without the concomitant use of topical steroids, indicating the importance of cytokine-mediated pruritus in the development of AD.

IL-4/IL-13

IL-4 and IL-13 are canonical type 2 cytokines that play key roles in the pathogenesis of AD by acting on various immune cells and epithelial cells (Wang and Kim, 2020). Recently, the involvement of these cytokines in pruritus has been noted through studies that IL-4 and IL-13 directly stimulate sensory neurons. (Campion et al., 2019; Oetjen et al., 2017). IL-4 has also been reported to enhance the responsiveness of multiple itch-sensory neuronal subsets to various pruritogens, such as chloroquine, histamine, IL-31, and TSLP (Oetjen et al., 2017). In support of these diverse effects of IL-4 and IL-13 on itch sensation, the mRNA of *IL4RA*, which encodes the shared receptor subunit for both IL-4 and IL-13, is expressed in a variety of itch-sensory neurons (Usoskin et al., 2015).

Dupilumab, a humanized anti–IL-4Rα mAb, demonstrated an improvement in pruritus via clinical trials for AD. Silverberg et al. (2020c) collected and analyzed data from two phase 3 trials (SOLO 1 and 2) to evaluate the effect of dupilumab on pruritus in adult patients (n = 1,379) (Silverberg et al., 2020c). Notably, the SOLO 1 and 2 trials tested dupilumab as a monotherapy, unlike other AD studies (AD-ADOL and CHRONOS). The researchers defined clinically meaningful improvement in pruritus as a 3- to 4-point improvement from baseline in the peak pruritus score on the numerical rating scale (NRS) between days 2 and 15. By day 4, more patients who received dupilumab (300 mg, once weekly) were more likely to have a ≥3-point improvement in their peak daily NRS score for pruritus than those who received placebo (7.4% vs. 2.9%). All patients who received dupilumab showed a significant improvement of peak daily

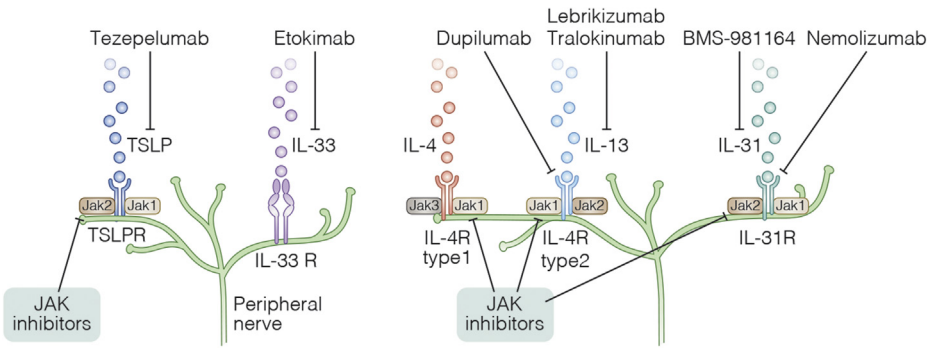

Figure 2. A variety of molecularly targeted drugs have been in use or under development to treat AD. From left to right and top to bottom: tezepelumab is a humanized mAb that binds to TSLP, inhibiting its interaction with TSLPR. Etokimab is a humanized anti-human IL-33 mAb. Dupilumab is a humanized mAb that targets IL-4Rα, common to both IL-4R complexes: type 1 (IL-4Rα/γc; IL-4–specific) and type 2 (IL-4Rα/IL-13Rα1; IL-4– and IL-13–specific). Lebrikizumab and tralokinumab are humanized mAbs against IL-13. BMS-981164 was an anti–IL-31 mAb targeting circulating IL-31, but it is no longer listed in the development pipeline. Nemolizumab is a humanized anti–IL-31RA mAb. Jak inhibitors inhibit the Jak-STAT signaling pathways downstream of TSLPR, IL-4R, or IL-31R. AD, atopic dermatitis; STAT, signal transducer activator of transcription; TSLPR, TLSP receptor. *Illustration assistance provided by katierisvicari.com.*

scratch NRS score compared with placebo during the period from day 4 to day 15. Thus, dupilumab can rapidly reduce persistent pruritus in some patients with AD.

Moreover, two IL-13–targeting antibodies, lebrikizumab and tralokinumab, are also in phase 2 clinical trials for the treatment of AD, where each has been efficacious for pruritis (Guttman-Yassky et al., 2020; Wollenberg et al., 2019).

IL-31

In 2004, IL-31 was identified as the first cytokine to function as a pruritogen and was initially demonstrated to be synthesized by activated $CD4^+$ helper T cells (Dillon et al., 2004; Szegedi et al., 2012). Thereafter, various immune cells other than T cells (e.g., monocytes, macrophages, DCs, basophils, and mast cells), as well as non-immune cells (e.g., KCs and dermal fibroblasts), have been demonstrated to be potential sources of IL-31 (Cevikbas et al., 2014; Cornelissen et al., 2012a; Niyonsaba et al., 2010; Petra et al., 2018; Raap et al., 2017). Recent literature has suggested the key involvement of IL-31 in the symptomatology of acute and chronic pruritus. Patients with AD exhibit greater amounts of IL-31 in the serum and tissue than healthy subjects (Lu et al., 2018; Neis et al., 2006). In addition, increased production of IL-31 from distinct T-cell subsets is also reported in the skin lesions of patients with AD (Szegedi et al., 2012). Two agents targeting IL-31 (lokivetmab and BMS-981164) have been developed, but despite the veterinary use of lokivetmab, there is no suitable use for humans.

Another way to target IL-31 signaling is through the receptor for this cytokine. IL-31 receptor is a heterodimeric complex composed of IL-31RA and OSMR. IL-31 receptors are expressed on various cells, including peripheral nerves, KCs, and immune cells (Cornelissen et al., 2012a). In addition to the direct effect on peripheral nerves, IL-31 has negative effects on KC differentiation by reducing the expression of molecules for skin barrier formation, possibly via IL-1 signaling, which can further promote skin pathology (Cornelissen et al., 2012b; Hänel et al., 2016).

Multiple clinical trials have now demonstrated the antipruritic effect of nemolizumab, a humanized anti-human IL-31RA mAb, for patients with AD (Kabashima et al., 2020, 2018; Nemoto et al., 2016; Ruzicka et al., 2017; Silverberg et al., 2020a). Targeting IL-31 receptor signaling aims to decrease pruritis and skin inflammation, which may reduce severity of eczema. In a phase 3 trial among Japanese patients, improvements in visual analog scale (VAS) scores were reported as early as day 2 (−10.3% with 60 mg nemolizumab [n = 143] and −4.4% with placebo [n = 72]) (Kabashima et al., 2020). In this study, nemolizumab produced a robust reduction in pruritis (−42.8%) compared with placebo (−21.4%) at week 16. As a secondary endpoint at week 16, the mean percent change of the Eczema Area and Severity Index (EASI) score was −45.9% with nemolizumab versus −33.2% with placebo.

The antipruritic efficacy of nemolizumab as a monotherapy in AD has also been demonstrated in phase 2 trials for 12 weeks (n = 264), where patients were randomly assigned to nemolizumab or placebo every 4 weeks (Ruzicka et al., 2017). Briefly, changes on the VAS scores at week 12 were −63.1% in the nemolizumab group (2.0 mg/kg of body weight) versus −20.9% in the placebo group. As a secondary endpoint, changes on the EASI at week 12 were −40.9% in the nemolizumab group versus −26.6% in the placebo group. Although comparison between two different clinical studies with nemolizumab and dupilumab cannot reach a conclusion, IL-31–targeting therapy seems to be specifically efficacious for pruritus, whereas IL-4/13–targeting therapy appears to show better clearance of skin inflammation alongside itch, suggesting the varying pathophysiologic roles of IL-4/13 and IL-31 in AD.

IL-33 and TSLP

IL-33 and TSLP are key proinflammatory mediators released from disrupted KCs of AD skin lesions. Recent reports have shown that IL-33 and TSLP may induce pruritus by activating peripheral nerves (Liu et al., 2016; Wilson et al., 2013). Intradermal injection of TSLP has evoked pruritus via activation of TRPA1 on sensory neurons in mice (Wilson et al., 2013). Although it is unknown whether IL-33 induces acute pruritus per se, dorsal ganglion cells express ST2, a receptor for IL-33, and anti–IL-33 and anti-ST2 antibodies attenuate scratching behavior in a murine model of contact allergy induced by poison ivy (Liu et al., 2016). These data suggest the possible

involvement of IL-33 and TSLP in the itch sensation of patients with AD.

Chen et al. (2019) conducted a phase 2a proof-of-concept study of etokimab (ANB020), a humanized antihuman IL-33 mAb, in 12 adult patients with AD. In subjects that received 300 mg etokimab intravenously one week after placebo injection, 83% of patients achieved the primary endpoint of EASI 50 on day 29, with a concurrent improvement in the percentage of the five-domain (5-D) itch scale score relative to baseline. In ATLSA, a phase 2b multidose study with etokimab or placebo (n = 300), however, each etokimab dosing arm has failed to meet the primary endpoint of percent change in the EASI from baseline to week 16 (ClinicalTrials.gov Identifier: NCT 03533751), and etokimab is no longer tested for AD.

Efficacy of an anti-TSLP mAb (tezepelumab) on AD was evaluated in phase 2 clinical trials, where mixed results for its efficacy on pruritus were found. A phase 2 trial, in which 113 patients were enrolled and received subcutaneous tezepelumab 280 mg or placebo every 2 weeks with topical corticosteroid, showed that a higher, but not statistically significant, percentage of tezepelumab-treated patients achieved an EASI 50 response at week 12 compared with the placebo group (Simpson et al., 2019). In contrast, tezepelumab demonstrated significant improvements of the patient-reported pruritus NRS outcome from baseline to week 12 (35.5%) versus placebo (21.0%). In contrast, although peak pruritus NRS scores were lower for tezepelumab-treated patients at week 12, they did not reach statistical significance. Moreover, little improvement in the 5-D pruritus scale score was observed. The efficacy of anti-TSLP antibodies in comparison with other biologics needs to be further examined (Nakajima et al., 2020).

Hence, in contrast to the efficacy of anti—IL-4RA and anti—IL-31R neutralizing antibodies, either TSLP- or IL-33—targeting therapy seems insufficient for controlling itch in AD. Blockade of one molecule, TSLP or IL-33, may not be sufficient to inhibit type 2 skin inflammation and pruritus (Imai, 2019; Kim et al., 2013). The difference in the efficacy on pruritus among cytokines also implicates the critical roles of IL-4/13 and IL-31 in inducing pruritus in AD.

Jak—signal transducer and activator of transcription signaling pathway

Various cytokines, including the type 2 cytokines such as IL-4, IL-13, and IL-31, exert their effects via the Jak—signal transducer activator of transcription (STAT) pathway (O'Shea and Plenge, 2012). Although Jak inhibitors are commonly used for the treatment of inflammatory diseases, such as rheumatic arthritis, lately they are attracting more interest as a therapy for inflammatory skin disorders, such as AD and psoriasis. (Fowler and Yosipovitch, 2020). Furthermore, both oral and topical Jak inhibitors demonstrated potent antipruritic properties in patients with AD in clinical trials as described below.

Baricitnib selectively inhibits Jak1 and Jak2. Simpson et al. (2020) collected and analyzed data from two phase 3 trials of randomized monotherapy (BREEZE-AD 1 and 2) of baricitinib in patients with AD (n = 1,239). There was a significant improvement of ≥4 points in peak pruritus NRS scores by 1 week and continued to improve through week 16 in patients treated with 4 mg baricitinib (21.5 %) compared with placebo (7.2 %).

Upadacitinib, an oral selective Jak1 inhibitor, had proved its antipruritic effect on AD in two phase 3 monotherapy trials (Measure Up 1 and Measure Up 2) (Guttman-Yassky et al., 2021). Here, the proportion of patients who had a 4-point or greater improvement in peak pruritus NRS score from baseline was higher in the upadacitinib 15 mg/day and 30 mg/day groups than the placebo group at weeks 1, 4, and 16.

Abrocitinib, another oral Jak1 selective inhibitor, demonstrated its efficacy on AD in a phase 3 monotherapy trial (n = 391) (Silverberg et al., 2020b). Briefly, greater proportions of patients in the 200 mg/day and 100 mg/day abrocitinib groups versus the placebo group achieved peak pruritis NRS improvement of ≥4 points at week 12 (55.3% and 45.2% vs. 11.5%). Bieber et al. (2021) have conducted a double-blind phase 3 trial (n = 838) of abrocitinib to compare with dupilumab and showed the superiority of the 200-mg dose, but not the 100-mg dose, of abrocitinib to dupilumab with respect to the improvement of ≥4 points in peak pruritus NRS score at week 2 (49.1% and 31.8% vs. 26.4%). This study suggests a critical role of Jak1 in the development of pruritus in AD.

The efficacy of topical Jak inhibitors on pruritus in AD have also been proved. Nakagawa et al. (2020) conducted a randomized phase 3 clinical trial to test the efficacy of topical ointment of 0.5% delgocitinib, a pan—Jak inhibitor, on pruritus in patients with AD. Here, NRS score in the 0.5% delgocitinib group was significantly lower than in the vehicle group at week 1, which lasted over 4 weeks. Another topical agent of ruxolitinib, a selective Jak1 and Jak2 inhibitor, demonstrated antipruritic efficacy on pruritus in AD in two phase 3 studies, TRuE-AD1 and TRuE-AD2 (Papp et al., 2021). Patients with AD were randomized 2:2:1 to twice daily 0.75% ruxolitinib cream, 1.5% ruxolitinib cream, or vehicle cream for 8 continuous weeks. Significantly greater reductions in itch NRS scores versus vehicle were observed within 12 hours of the first application of 1.5% ruxolitinib cream; further reductions were observed over 8 weeks with ruxolitinib cream regimens in a strength-dependent manner.

These studies proving the efficacy of Jak inhibitors suggest the critical role of the Jak-STAT pathway, especially Jak1, in the development of pruritus in AD. Considering the broad range of cytokines utilizing the Jak-STAT pathway, it is possible that yet unidentified cytokines could activate neuronal pruritus through this pathway.

CYTOKINE-MEDIATED ITCH IN OTHER PRURITIC SKIN DISORDERS

The efficacy of antipruritic therapies targeting cytokine-mediated signals has also been demonstrated in other chronic pruritic skin disorders, such as prurigo nodularis. Although dupilumab is FDA-approved for the treatment of moderate-to-severe AD, the antipruritus effect of dupilumab on prurigo nodularis has been demonstrated in observational studies (Beck et al., 2019; Giura et al., 2020; Naafs and Alemu Belachew, 2020). Currently, dupilumab is being tested for prurigo nodularis in a phase 3 clinical study (PRIME) (ClinicalTrials.gov identifier: NCT 04183335).

Nemolizumab has also demonstrated efficacy on severe pruritus in patients with moderate-to-severe prurigo nodularis in a recent randomized phase 2 clinical trial (Ständer et al., 2020). The primary outcome of percent change from baseline at week 4 in the mean peak score for pruritus on the NRS was reduced by 53.0% with nemolizumab (n = 34) versus 20.2% with placebo (n = 36). The efficacy of oral Jak inhibitors has also been reported on chronic pruritus of unknown origin (Oetjen et al., 2017; Wang et al., 2019).

Hence, therapeutic strategies targeting cytokine-mediated signaling could be a key to help patients suffering from chronic pruritic skin disorders.

CONCLUSION

Despite pruritus being a common complaint in the dermatological field, many patients are refractory to available therapies. Currently, many drugs targeting itch-inducing cytokines are under development, and some of them are effective in controlling the signs and symptoms of pruritus. Therefore, new therapies focused on cytokine-mediated pruritus are expected to bring about dramatic changes in patient outcomes over the next few years.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: RS, NK; Project Administration: KK; Visualization: RS, RTI; Writing - Original Draft Preparation: RS, NK; Writing - Review and Editing: NK, RTI, KK

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