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REVIEW ARTICLE

# Reviewing the use of corticosteroids in bronchopulmonary dysplasia[☆],[☆☆]

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**Abstract**

*Objective:* Review the risks and benefits of postnatal corticosteroid use for the treatment of bronchopulmonary dysplasia, considering that there is not a more effective therapy.

*Data sources:* The literature review was carried out in the BIREME database, using the terms ''bronchopulmonary dysplasia and corticosteroid'' in the LILACS, IBECS, MEDLINE, Cochrane Library, and SciELO databases, selecting the most relevant articles on the subject, with emphasis on recent literature published in the last five years.

*Summary of the data:* In preterm infants, bronchopulmonary dysplasia is still a common problem and remains without a specific therapy, despite knowledge of the several risk factors. The treatment essentially consists of supportive measures, but in the past, corticosteroids were widely used, as they are the only medications that have an impact on disease progression. However, the emergence of cerebral palsy associated with the indiscriminate use of corticosteroids has prevented the prescription of this drug in the last 15 years. Since then, no new measures have been taken, and the incidence of the disease tended to increase during this period, creating the need for a review of corticosteroid use and, possibly, more restricted indications.

*Conclusions:* The association between risks and benefits of corticosteroid use in preterm infants needs to be considered due to the fact that some infant subpopulations may show more benefits than risks, such as those using mechanical ventilation with difficult weaning.

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**PALAVRAS-CHAVE**
Displasia
broncopulmonar;
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Tratamento

### Revendo o uso dos corticosteroides em displasia broncopulmonar

#### Resumo

*Objetivo:* O objetivo desse estudo é revisar os riscos e benefícios do uso do corticoide pós-natal para o tratamento da displasia broncopulmonar, uma vez que ainda não há outra terapia mais eficaz.

*Fontes de dados:* A revisão da literatura foi realizada pelo banco de dados da BIREME, utilizando os termos *bronchopulmonary dysplasia and corticosteroid* nos sistemas LILACS, IBECS, MEDLINE, Biblioteca Cochrane, SciELO, sendo selecionados os artigos de maior relevância sobre o tema, com ênfase na literatura dos últimos cinco anos.

*Síntese dos dados:* Em recém-nascidos prematuros, a broncodisplasia ainda é um problema frequente e sem terapêutica específica, apesar do conhecimento dos vários fatores de risco. O tratamento, basicamente, é feito por medidas de suporte, mas o corticoide no passado foi largamente utilizado por se tratar da única medicação com impacto na evolução da doença. Porém, o aparecimento de paralisia cerebral associada ao uso indiscriminado do corticoide inviabilizou a prescrição da droga nos últimos 15 anos. Desde então, nenhuma nova medida foi tomada e a incidência da doença tendeu a um aumento neste período, criando a necessidade da revisão do uso do corticoide e de possíveis indicações mais restritas.

*Conclusões:* A relação do risco e benefício dos corticoides utilizados em recém-nascidos prematuros precisa ser ponderada diante de algumas subpopulações de bebês que podem ter mais benefícios que riscos, como naqueles em ventilação mecânica e com desmame difícil.

## Introduction

Despite perinatal care improvement and greater survival of increasingly young infants, bronchopulmonary dysplasia (BPD) is still a common complication and one of the most prevalent and important sequelae of prematurity. Between 2008 and 2013, the records of the Rede Brasileira de Pesquisas Neonatais (Brazilian Network of Neonatal Research) showed that, despite the improved survival of extremely preterm infants, the incidence of BPD ranged from 14.7% to 14.0%, remaining virtually unaltered.[1]

Better prenatal conditions, early surfactant replacement, oxygen supplementation, mechanical ventilation, better invasive and non-invasive monitoring, total parenteral nutrition, and extracorporeal membrane oxygenation are examples of neonatology advances in the last four decades, but unfortunately little has changed regarding BPD prevention or treatment.[2]

BPD predisposes to increased hospital length of stay and increases neonatal mortality. During childhood, dysplastic infants have worse neurodevelopment and prolonged hospitalizations, in addition to the possibility to have impaired lung function throughout life.[3] Furthermore, the disease represents a major burden on the family structure of these children, in addition to the negative impact on public health resources.

The wait for new therapeutic measures has not been a promising one, which forces researchers to try to better understand the risk factors and preventive measures for BPD. Once disease onset has occurred, the treatment is mostly restricted to support measures, because the proposed therapies in recent years have not altered disease evolution. Among these therapies, corticosteroid administration is the most controversial; its use started to decrease in the 2000s, when it was believed that the risks of using corticosteroids were greater than their benefits. Some authors, however, attribute this decrease to the rise in BPD incidence. Thus, given the lack of new therapeutic options, corticosteroids are causing controversy once again, generating new insights on their application.[2,4]

## Risk factors

Several risk factors are involved in the development of BPD; however, it is difficult to define which one is the most important, as they interact in different ways during the different stages of preterm newborn development. Moreover, not all preterm infants develop BPD, as individual responses to lung lesions are modulated by genetics, epigenetics, and by combining different disease protection and resilience factors.[4]

BPD is essentially the product of tissue inflammatory response caused by its own repair. As the lung is constantly developing, not only in the fetus, but also in the newborn, understanding the potential lesions that can occur greatly depends on the maturation phase the lesion. From alveolar septal fibrosis found in classic bronchopulmonary dysplasia, observed in later preterm infants, to the inhibition of pulmonary alveolus formation found in ''new dysplasia,'' observed in preterm infants younger than 32 weeks, there is a large spectrum of the same disease.[3–5]

The lung lesion process can be initiated while still *in utero*; the best known factors are: intrauterine growth restriction, lack of antenatal corticosteroids, chorioamnionitis, and gestational hypertensive disease.[3,6,7]

Male gender, lower gestational age at birth, as well as barotrauma and excessive oxygen supplementation in the delivery room are early risk factors.[7,8] Mechanical ventilation, hyperoxia, and neonatal infections are factors that trigger an inflammatory process, which in the presence of an immature lung represent the main pillars of the disease physiopathology. In a review article, Bhandari[4] mentions that preterm infants with lungs at the canalicular/saccular stage of development are more likely to develop BPD and that the three abovementioned factors (mechanical ventilation, sepsis, and hyperoxia) are the main contributors to the disease pathogenesis. The author also suggests that it is more important to avoid neonatal systemic infections than mechanical ventilation in lung inflammatory response decrease, thus having a greater impact on the reduction of BPD incidence.

Genetics is an increasingly studied risk factor and may interfere in many different ways, interacting with external aggressions and the pulmonary maturation phase of the preterm infant. Let it be supposed, for instance, that a specific fetus has as genetic inheritance a particular allele of the gene of the superoxide dismutase (SOD) enzyme, which promotes susceptibility of the terminal bronchioles to oxygen free radicals. However, this susceptibility is programmed to occur from 24 to 28 weeks of gestation. If this fetus is born at 32 weeks of gestational age, their predisposition to BPD will be lower, not only due to increased lung maturity, but also the lower influence of the SOD gene at that particular time of fetal development.[9] If, on one hand, the complexity of these interactions prevents complete understanding the disease physiopathology, on the other, it creates the hope of new therapeutic perspectives for the future, with several research lines to be developed.

For now, there are still many questions and, despite the better understanding of BPD pathogenesis, few answers have been provided about the effectiveness of new treatments.[6,10]

Primary prevention of prematurity is still the best method to prevent BPD, but even with adequate prenatal care, it is not always possible to prevent preterm births and secondary prevention is then discussed as an attempt to prevent, or at least minimize, the damage caused by the disease.

## Prevention

The best time to start preventing BPD is still unclear, as it is not known when disease is triggered in each infant, and it may even be triggered during the fetal stage.[5] The incomplete knowledge of the disease's physiopathology, associated with the interactions of diverse and uncontrollable risk factors, prevent physicians from individualizing the appropriate therapy for each preterm infant. However, based on the existing knowledge of its physiopathology, fetal physiology, and the impact of early termination of a pregnancy, some measures have been studied and sometimes applied in clinical practice.[2,6,10]

The use of antenatal corticosteroids for pulmonary maturation decreases neonatal mortality, respiratory distress syndrome of the newborn (RDS-NB), and peri-intraventricular hemorrhage. Therefore, it is a formal recommendation for pregnant women in preterm labor.[11] But even in combination with postnatal surfactant, despite the abovementioned benefits, study results indicate that there was no decrease in the incidence of BPD.[6,10]

The association of barotrauma or volutrauma with BPD led to the search for better ways to ventilate the preterm infant, with gentler ventilation proposed, with the use of permissive hypercapnia and guaranteed volume as the ventilation mode. Despite the need for further studies, more physiological ventilation, with volume and low oxygen concentrations, without leading to hypoventilation, should be recommended.[8]

The caffeine used to treat apnea of prematurity has also shown to decrease the risk of BPD, although the action mechanism is yet to be clarified.[10] Köroğlu et al.[12] evaluated the effect of caffeine in preterm rats, using lipopolysaccharide as proinflammatory agent, and observed that there was an improvement in lung function, suggesting a protective effect through an anti-inflammatory mechanism. Moreover, the use of caffeine has been shown to increase the response of carbon dioxide chemoreceptors, improve respiratory muscle performance, and increase the central nervous system excitability.[6,10]

Vitamin A has several cell functions, acting as a potent antioxidant agent. In addition to the inability to metabolize and eliminate free radicals, preterm infants also have vitamin A deficiency.[6] When the vitamin is supplemented, up to the normalization of serum levels, it is possible to observe the decrease in oxygen dependence at 36 weeks corrected age. However, in the long term, there was no difference in the final outcome between infants who received high doses of vitamin A and those who did not.[13] Although encouraging, vitamin A supplementation is also hampered by the limited availability of the medication outside large centers.

Oxidative stress of injured cells releases free radicals. As free radicals are directly involved in BPD progression, prophylactic supplementation with antioxidant enzymes may be promising. Of all the antiradical treatments, the use of superoxide dismutase appears to be the most effective.[7] Davis[14] studied the intra-tracheal use of superoxide dismutase and demonstrated the minimization of the harmful effects of mechanical ventilation and oxygen use, with no associated toxic effects. McEvoy et al.[3] mention two other antioxidants: glutathione precursors and cimetidine, but to date, the studies have shown disappointing outcomes.

Inhaled nitric oxide improves oxygenation and ventilation in different situations, such as meconium aspiration syndrome, sepsis, and pulmonary hypertension, as well as showing anti-inflammatory properties. According to these findings, studies have been carried out to investigate the potential benefits of nitric oxide in reducing BPD risk or severity. However, evidence does not support the role of nitric oxide in preventing the disease, although it is not yet clear whether there is any specific subgroup of preterm infants that could benefit from this treatment.[6]

The association of patent ductus arteriosus (PDA) with BPD has been demonstrated as an association with the disease, and not as a causative factor. Some studies have shown that prophylactic closure of the ductus arteriosus does not prevent BPD, whereas some suggest that the treatment may even increase the risk to develop the disease. The use of indomethacin, while promoting the closure of the ductus arteriosus, may increase the incidence of BPD

when compared to spontaneous closure. Surgical intervention also showed no effect in preventing BPD, whereas better results were obtained when there was no intervention, neither pharmacological nor surgical therapy.[8] Nevertheless, these results are controversial and sometimes discordant. In Brazil, Sadeck et al.[15] evaluated 494 preterm infants with birth weight <1000 g and 33 weeks of gestational age, and concluded that both pharmacological and surgical treatments decreased the mortality in very-low birth weight preterm infants. However, a statistically significant difference was demonstrated regarding BPD incidence, demonstrating benefits in the conservative and pharmacological treatment groups in relation to the surgical treatment group, reinforcing the need to perform more randomized controlled trials to understand PDA in preterm infants.

Neonatal sepsis has a close association with BPD and is considered an independent risk factor, as well as mechanical ventilation and oxygenation. Lahra et al.[16] reported an increase in BPD in a cohort of 798 preterm infants with gestational age <30 weeks when, in the presence of chorioamnionitis, the infant showed associated neonatal sepsis. Differently from this result, preterm infants who did not develop neonatal sepsis, even when undergoing treatment for chorioamnionitis, had a lower incidence of BPD. Although the direct role of infection in the development of BPD is not completely understood, the evidence suggests that systemic inflammation, associated with vascular permeability alterations, is a major cause of cell injury and the consequent alveolarization process interruption.[5,7] Some animal studies suggest that preventing neonatal infection, localized or systemic (sepsis), is even more important in reducing the inflammatory response of the lungs than invasive mechanical ventilation. In other words, it is speculated that there might be an even greater impact in reducing BPD rates through neonatal infection control, even in patients undergoing invasive mechanical ventilation.[4]

Although some therapies may be suggested based on the knowledge of BPD predictors, it has not been sufficient to change the disease incidence over the years. Given this scenario, still an unclear one, corticosteroids are once again being discussed.

## Once again, the corticosteroid

Historically, the treatment of BPD has always been the main indication for corticosteroid use in neonatology, even though other indications, such as refractory shock and post-extubation laryngitis, are becoming frequent.

Since it was established that inflammation is a determinant for BPD, corticosteroids, for their potent anti-inflammatory action, have been widely studied as a therapeutic or prophylactic tool. The systemic use of corticosteroids not only reduces inflammation but also increases surfactant production, accelerates lung cell differentiation, reduces vascular permeability, and increases lung fluid resorption. These actions result in increased lung compliance and tidal volume, improving ventilatory function.[6,8] Regardless of the mechanism, corticosteroids have positive results in the treatment of preterm infants with BPD. The knowledge of these effects led to its abusive use,

especially in the late 1990s, when there was a tendency for its increasingly early use, even in less severe cases.[17]

The postnatal effectiveness of dexamethasone in the treatment of mechanical ventilation-dependent BPD was first demonstrated in 1983 by Mammel et al.[18] Over time and due to the promising results, the use of postnatal high-dose corticosteroids for extended periods of time became routine, particularly in extremely preterm infants, to the point of having a formal indication for BPD prevention. In Canada, between January 1996 and October 1997, 25% of very-low birthweight infants started receiving systemic corticosteroids in the first week of life. In the United States, this rate was 19% between 1995 and 1996.[19]

If in the short term, the early use of corticosteroids demonstrated decreased dependence on mechanical ventilation and oxygen as immediate benefits, in addition to the reduced incidence of BPD, it would be expected that, in the long term, there would also be a reduction in neurological sequelae associated with BPD. However, after more than a decade of widespread use of postnatal systemic corticosteroids, differently from what was expected, clinical trials started to demonstrate a significant increase in the incidence of cerebral palsy.[18]

Gradually, the adverse effects of treatment with corticosteroids were established: hyperglycemia, systemic hypertension, hypertrophic cardiomyopathy, digestive bleeding, gastrointestinal perforation, hypothalamic–pituitary–adrenal axis suppression, failure to thrive, decelerating head circumference growth rate, neurodevelopmental delays, and lung structure alterations.[2]

In 2010, Halliday et al. analyzed 28 clinical trials that compared the early use of postnatal systemic corticosteroids in 3740 participants. They found that the group receiving dexamethasone showed earlier extubation, decreased mortality, and reduced incidence of pulmonary disease, when evaluated at both 28 days of life and at 36 weeks corrected age. There was no difference between treatment and control groups regarding neonatal infection, severe peri-intraventricular hemorrhage, peri-intraventricular leukomalacia, necrotizing enterocolitis, and pulmonary hemorrhage. However, there was a prohibitive increase of cerebral palsy cases in the treatment group (RR: 1.45, 95% CI: 1.06–1.98).[20] Nevertheless, it is noteworthy that these reported adverse effects are based on studies with high-dose dexamethasone administered in the first days of life and maintained for extended periods.

After 2002, the use of corticosteroids was formally discouraged by the American Academy of Pediatrics and the Canadian Pediatric Society (Committee on Fetus and Newborn, 2002), although some authors have pondered that a prudent assessment of the available data should have been conducted before the formal drug contraindication.[21] Nonetheless, what happened was exactly the opposite, and there was a sudden interruption of all studies related to the use of postnatal corticosteroids. The fact is that, at that time, no distinction was made between treatments with early and indiscriminate use of corticosteroids and their later use, with more specific indications.[17]

In 2003, Halliday et al. began studying the use of corticosteroids in relation to the time of therapy onset, classifying the treatment in three different subgroups: early, for the use within the first 96 h of life; moderately early, for the

use between seven and 14 days of life and; late, for the use after two weeks of life.[22,23] The authors confirmed that early administration of corticosteroids, despite the immediate improvement in patient's ventilation, should be proscribed because of its association with the high risk of cerebral palsy.

Moderately early administration was evaluated in seven randomized clinical trials with a sample of 669 patients, showing better ventilatory weaning and decreased BPD incidence, similar to that found with early corticosteroid administration. They also reported that adverse effects, such as hypertension, hyperglycemia, gastrointestinal hemorrhage, hypertrophic cardiomyopathy, neonatal infection, and mainly, neurodevelopmental alterations, were not observed.[22]

The meta-analysis of dexamethasone use after the third week of life consisted of nine randomized clinical trials, resulting in a total of 562 studied patients. The group that used corticosteroids had lower rates of extubation failure and BPD incidence. The observed short-term adverse events were: increase in blood pressure, urinary glucose levels, and slight increase in retinopathy of prematurity severity, but no increase in cases of blindness. There was no difference between the groups regarding infection, enterocolitis, and gastrointestinal bleeding. In the group that used corticosteroids, no neurodevelopmental delay was observed, although there are limitations in the used methodology for the long-term assessment of these children in some of these clinical trials.[23]

Although none of the studies with dexamethasone use after seven days of life showed an increased risk of cerebral palsy, the authors recommend caution in the indication of corticosteroids, reserving them for cases with greater difficulty in mechanical ventilation weaning, also recommending smaller doses and the shortest possible time of use.[20,22,23]

The problem in creating a guideline for clinical practice based on interpretations of these randomized clinical trials is that there may be overlapping of two confounding factors. The first factor is that the effects of corticosteroids, both beneficial and adverse, as well as with any other drug, are sensitive to the dose and treatment duration. The second factor is related to prematurity, as the fetus or newborn are at different developmental stages, which probably results in different susceptibility to the effects of corticosteroids. For instance, given the knowledge that preterm infants are more unstable in the first days of life and knowing that severe events, such as peri-intraventricular hemorrhage, are more likely to occur in the first week of life, it is possible that the adverse effects of corticosteroids may be exacerbated by the infant's postnatal age. These two factors may also be potentiated by other risk factors for BPD. In this scenario, the return of corticosteroids opens new discussions.[17]

As the indiscriminate use of corticosteroids in the 1990s increased the cases of cerebral palsy, their sudden disuse in the 2000s reflected in the increasing incidence of BPD, especially in very-low weight preterm infants.[19]

Both prematurity and BPD, as well the corticosteroid use, are associated with worsened neurological development, and it is likely that the negative results of early steroid use to prevent BPD may vary according to disease incidence in the control group.[24,25] That is, the negative impact of early use of corticosteroids is inversely proportional to BPD incidence. A group with low incidence of BPD would show more

harm than good as a result of early corticosteroid use. However, if the incidence of BPD is high in this population, there will be a higher incidence of survivors without neurological impairment. Considering this hypothesis, in 2006 Doyle et al.[25] re-evaluated the effect of early use of steroids in preterm infants, based on 20 randomized controlled trials. The authors also assessed the effects of corticosteroids in the long term (at least up to 12 months of chronological age) in 14 of the 20 selected clinical trials. Through analysis by meta-regression, the authors correlated the results of clinical trials with some of the most important risk factors for the development of BPD and found an alternative explanation for the adverse effects of early treatment of corticosteroids in preterm infants. The explanation is that corticosteroids do not have only direct harmful effects, but also, by promptly improving pulmonary function, indirectly improve brain development. Thus, future studies must find the line of demarcation, below which the risks of treatment with corticosteroids would overlap the risks of the disease.[17] In 2014, the authors extended the meta-analysis with the latest six new clinical trials and suggested the use of risk predictors to guide the decision of using corticosteroids in the treatment of BPD in mechanical-ventilation dependent preterm infants.[25]

During the preterm infant's follow-up, several triggers of the systemic inflammatory response can interact with each other, even with one or more of these factors, potentiating the injuries. Neonatal sepsis associated with chorioamnionitis occurs simultaneously with the early use of corticosteroids, and both interact with bronchopulmonary dysplasia, making it difficult to recognize the contribution of each factor in the development of cerebral palsy. Hentges et al.[26] evaluated 94 preterm infants with very-low birth weight and neonatal sepsis and were able to associate the infection with an increased ventilatory support time, longer hospital stays, and higher incidence of bronchopulmonary dysplasia and seizures.

Another consideration is that most of the early studies were with patients using high-dose dexamethasone with early treatment onset and prolonged duration. Some of these patients started corticosteroids before 72 h of life, more as prevention than treatment of BPD, and continued its use for up to 42 days of life.[17]

Titration of the ideal dose for the use of corticosteroids is also subject to debate. The first clinical trials used a standard dose of 0.5 mg/kg of dexamethasone, which was reduced slowly over several weeks. The most recent clinical trial used lower initial doses of 0.2, 0.15, or 0.1 mg/kg, in decreasing doses, during seven to 10 days; the treatment was terminated if there was no therapeutic response.[16]

In recent years, the role of other corticosteroids, rather than dexamethasone, has been questioned regarding their use in BPD prophylaxis or treatment. Because hydrocortisone is a natural hormone, its higher degree of safety was postulated when compared to dexamethasone. Watterberg et al.[27] evaluated the use of hydrocortisone for the prophylaxis of early adrenal insufficiency, aiming at BPD prevention. The study was carried out in preterm infants weighing <1000 g with mechanical ventilation, randomized into two groups, with and without hydrocortisone. The study had to be terminated due to the increase in cases of intestinal perforations. However, in cases that had already been

concluded, there were no significant differences for mortality and BPD, except in those exposed to chorioamnionitis, which showed lower mortality and lower incidence of BPD when treated with hydrocortisone.

Finally, the search for steroids with the same therapeutic effect and fewer adverse effects than dexamethasone continues. The inhaled route, for instance, seemed promising due to two advantages: direct drug action on the inflammation site and rapid action onset, with low doses and less systemic absorption. However, there is very little evidence of the efficacy of inhaled corticosteroids to justify their routine use.[28] A clinical trial started in 2009 and still in progress, proposes the study of 850 infants between 23 and 27 weeks corrected age, randomized within 12 h of life into two groups: inhaled budesonide *vs.* placebo. This study, known as NEUROSIS (Neonatal European Study of Inhaled Steroids), will evaluate survivors without BPD as the primary outcome, when they reach 36 weeks corrected age. Subsequently, the study participants will be followed for the neurological outcome up to 18–22 weeks corrected age. Additional pharmacodynamics studies and a study excerpt to assess genetic susceptibility will also be performed in the future.[29]

In 2008, Yeh et al.[30] published a pilot study on the use of budesonide instilled directly into the trachea and distributed to the lung periphery through the surfactant. Preliminary results showed no significant difference in the incidence of BPD or mortality when assessed alone. However, after combining the two outcomes, death and BPD, the best results were observed in the treatment group. Currently, Yeh et al. are replicating the same study at multicenter level.

## Conclusion

Given the abovementioned facts, it is now time to discuss preterm subpopulations with clear indications for the use of corticosteroids in the treatment of BPD. Preterm infants, on mechanical ventilation and showing difficulty in weaning, are probably the starting point for further research.

In the neonatal intensive care unit at Hospital das Clinicas, Universidade Federal de Goiás, systemic corticosteroids are used in selected cases. The criteria are: preterm infants on mechanical ventilation for more than two weeks, showing difficulty in weaning from mechanical ventilation, after excluding other causes, such as sepsis, shock, congenital malformations, and central nervous system depression. The corticosteroid of choice is dexamethasone and treatment is initiated at a dose of 0.20 mg/kg/day, divided into two daily doses, which are reduced every three days to 0.15 mg/kg/day and finally, 0.10 mg/kg/day. The treatment is discontinued if the patient does not show any clinical improvement up to the 3rd day of use.

The fact is that, in the absence of alternatives, in some manner corticosteroids will continue to be used in the perinatal period. It is important to understand that, when using corticosteroids for the treatment of BPD, physicians should not be deluded by the immediate benefits only. And after selecting the group that fits in the treatment, the risks of adverse effects of corticosteroid use in the long term should not be forgotten, especially those related to neurodevelopment. While the results of studies and new treatment proposals are awaited, prematurity prevention, risk factor identification, and the judicious use of corticosteroids in specific populations are the only tools available.

## Conflicts of interest

The authors declare no conflicts of interest.

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