CURE Asthma: a unique opportunity for Australia

Asthma is a distressing ... malady; the patient lives in dread of the attacks, which are relieved but not cured by treatment. William Osler, 1892¹

Can my asthma be cured? No, there is not yet a total cure for asthma. *Global Initiative for Asthma*, 2025²

s asthma fundamentally incurable? We would not accept this proposition for most serious diseases. Cancer researchers seek to cure cancer. Yet Osler's dictum, penned more than a century ago, and clinical experience during the asthma crises of the 1960s, 1980s, and 1990s, during which the incidence and prevalence of asthma remained stubbornly high and its severity and mortality increased, have engendered this pessimism. Despite significant recent progress in its management, the widely held view is that asthma is a treatable but incurable disease.

We cannot accept this situation. The burden of asthma in Australia, among the highest in the world,⁴ is too great and the need for solutions too compelling. Patients, clinicians, and researchers want cures. 5,6 They have been achieved for other diseases; why not asthma? The CURE Asthma initiative challenges the pessimism that it is incurable. Its goal is to eliminate asthma by discovering curative therapies. To do this we have declared our bold but realistic ambition to cure asthma and have established a national roadmap of translational research that will deliver new therapies that reverse the fundamental molecular causes of the different forms of asthma. We argue that research, industry, technology, innovation and government bodies in Australia be brought together and that the technical and financial resources needed for sustained discovery and translational research to find cures be provided.

The CURE Asthma initiative was developed by Asthma Australia as the result of its research prioritisation consultations with patients and their carers and academic, policy, and government bodies regarding the 2023 National Asthma Research Agenda. These consultations focused on important practical aspects of asthma management, including improving day-to-day care. They remain pressing needs, but a bolder challenge was advanced during the 2023 consultations: should curing asthma be a priority? It is remarkable that, when the possibility of finding cures was shared with the Asthma Australia Consumer Advisory Council, the delegates responded: "we were always told it is incurable", and "why didn't we do this 30 years ago?" People with asthma and

their families want cures.

Just as the statement "we choose to go to the Moon" has become emblematic of world-changing research, we propose that declaring the ambition to CURE asthma will open the imagination to transformative solutions. The purpose of this supplement is more than to provide a brief narrative of how and why the CURE Asthma Initiative was established. It is also more than to lionise the world-leading position of Australia in advanced asthma research, built on decades of medical research support that has established exemplary longitudinal clinical cohorts, among the longest established and best characterised in the world, but a barely tapped resource. CURE Asthma is more than the outline of our research program, the scientific rationale and immense promise of which is explored by field experts in the articles comprising this supplement. The purpose is, like the United States *National Cancer Act* of 1971, a call to arms, to imagine a moonshot.

The size of the problem and the opportunity

We call for no more me-too medicines but a commitment to develop treatment approaches that focus on prevention and cure. *Lancet Commission*, 2018.⁵

A cure for asthma would not only transform our daughter's life but also our family's. It would free my daughter from the constant battles she faces, not just with her health but also with missing out on school, activities and having a carefree childhood. *Mother of "Oakley", New South Wales*, 2024.

Although many people believe the asthma problem is now under control,⁵ given the major improvements

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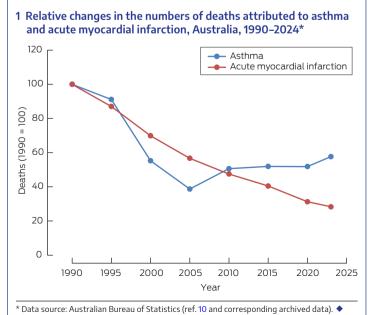
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in care introduced from the 1990s to the 2010s, ^{8,9} the burden of asthma remains unacceptably high, death rates are again rising (Box 1), and there are no disease-modifying or curative therapies. Funding of basic research into the fundamental molecular mechanisms of asthma, especially of mild and moderate disease, is low given the burden of disease. ¹¹⁻¹³ Many people with asthma and their clinicians simply accept that they must live with their symptoms, exacerbations, and often permanent damage and lifetime sequelae. ¹⁴ This cannot continue.

Despite widespread complacency, asthma remains a major health problem in Australia, affecting about 2.8 million people (11% of the population), one of the highest prevalence rates in the world (United States, United Kingdom: about 8%). ^{15,16} Its prevalence is particularly high among children, First Nations people, and the socio-economically disadvantaged. ¹⁷ About 400 000 children have asthma, making it the leading cause of disease burden among those aged 0–14 years, and it is the cause of more hospitalisations of children than any other chronic condition. ^{9,17,18} Children of pre-school age with asthma are 87% more likely than other children to develop anxiety disorders in later childhood, ¹⁹ and children hospitalised with asthma are more likely to fall behind academically. ²⁰

Further, asthma outcomes are strongly influenced by social determinants of health; its prevalence and disease burden are linearly correlated with social deprivation.^{17,21} Social determinants influence asthma both directly, by increasing disease susceptibility, and indirectly, through the hazards of exposures and insults, access to health care, nutrition, and lifestyle factors. Despite great resilience and the remarkable examples of Aboriginal community-controlled progressive health care models, the difficulties experienced by Aboriginal and Torres Strait Islander people are particularly great²² (Box 2).

A 2016 online survey of 1333 adults with severe asthma and caregivers of children with severe persistent asthma from nine countries found that its impact on quality of life, asthma control, exacerbations, and psychological wellbeing had not changed since a similar 2004–05 survey, despite the introduction of targeted biological pharmaceuticals.³⁰ Mild and moderate asthma also cause a substantial health burden for the general population. A 2021 Australian Bureau of Statistics survey found that people with asthma were less likely to report very good or excellent health.³¹ International surveys have also found that people with asthma are more likely to report psychological distress than respondents without asthma or with other health conditions. 32 In 2023, asthma caused more than 30000 hospitalisations in Australia, ³³ 97 000 emergency department visits, ³⁴ and 474 deaths, ¹⁰ contributing to an estimated economic cost exceeding \$28 billion, \$24 billion of which was attributed to the aggregate burden experienced by

2 What CURE might mean for First Nations Australians*

Before the arrival of the British colonisers, First Nations peoples participated in active lifestyles, accessed food sources high in nutrition and maintained sustainable ecosystems while caring for Country. The impact of colonisation, and ongoing settler colonialism, has contributed to the precipitous decline in Aboriginal and Torres Strait Islander health status over the last 230+ years. Historical, political, social, and economic factors, which frame both the past and present burden of disease, have contributed to substantial Indigenous health inequities.

Aboriginal and Torres Strait Islander peoples experience higher rates of chronic conditions such as diabetes, cardiovascular disease, and renal disease, which are avoidable conditions linked to the destruction of traditional cultures during colonisation, and contemporaneously, to the social determinants of Indigenous health, including history, settler colonialism, racism, intergenerational trauma, family, community, identity, and Country. These determinants are interwoven within broader mainstream social, political, and economic contexts in which First Nations people live.

Similarly, asthma is a serious condition experienced by First Nations peoples which often presents with other co-morbidities and risk factors. Yet despite this, respiratory disease, including asthma, receives less attention than other chronic conditions, despite high hospitalisation and mortality rates. This unfair and remediable imbalance will be potentially redressed by the remediable research of CURE.

Research remains a contested space given the ongoing inequities and injustices in Aboriginal and Torres Strait Islander health. Historically, health research has often been undertaken without appropriate engagement, self-determination, reciprocity, or respect, thus creating harm and little benefit for First Nations peoples. The research paradigm is gradually being transformed through privileging Aboriginal and Torres Strait Islander knowledge systems in collaborative approaches and with community ownership.

CURE has significant potential to alleviate asthma and close the gap for Aboriginal and Torres Strait Islander peoples for whom respiratory conditions may be extremely debilitating. The research team need to consider how they will meaningfully engage First Nations communities early in the CURE journey. This approach will include First Nations consumers and researchers, from the outset, in culturally appropriate ways to lead and embed Aboriginal and Torres Strait Islander perspectives.

It is critical for researchers to understand where, and for whom and how, asthma as a priority is positioned to facilitate meaningful engagement in research implementation, participation, and governance. Researchers should listen, learn, and evolve to become culturally safe and capable, in an environment where First Nations researchers may seek opportunities, and be leaders in the work. Non-Indigenous researchers will learn how to use new knowledge and skills in cultural safety to minimise the impacts of unconscious bias and power differentials, and to engage in critical reflection on the influence of their values, attitudes and cultural beliefs when engaging in research.

The research program over the 10 years will not only adhere to the Australian Institute of Aboriginal and Torres Strait Islander Studies (AIATSIS) guidelines but will also include the engagement of First Peoples at all stages so the findings and translation will truly reflect First Peoples outcomes, priorities, and communication needs (nothing about us without us).

Aunty Wendy Edmondson, 2024.

CURE Asthma First Nations Knowledge Holder

^{*}In keeping with current cultural practice, the terms "Aboriginal and Torres Strait Islander", "Indigenous", and "First Nations" are used interchangeably in this text.

This text was invited as an unreferenced narrative. Readers will find supporting information in references 23-29.

people with asthma.³⁵ This estimate did not include the large impact on parents and carers, and the figures also excluded the substantial morbidity and costs associated with treatment side effects, particularly those of systemic corticosteroid therapy, including osteoporosis, metabolic and endocrine disorders, glaucoma, hypertension, and increased infection risk.³⁶

These statistics only dimly reflect the challenges faced by clinicians. Childhood is often described as the silent years of asthma, as it is the period when diagnosis is difficult and objective tools for guiding treatment and assessing progress are few.³⁷ It is striking and unacceptable that we still do not have molecular diagnostic methods. Clinicians must rely on often unreliable symptom reports by parents,³⁸ as validated biomarkers and lung function tests for young children are limited. Further, childhood is a critical period of lung development. Even if diagnosis is optimised, no therapy modifies the disease course.⁵ Inhaled corticosteroids, the usual standard of care, suppress inflammation and are effective, 39 but their typically intermittent use does not eliminate symptoms, completely prevent exacerbations in the long term, or alter the trajectory of the disease.⁵ Inhaled corticosteroids can be lifesaving but they are not curative.

In adulthood, by which time much of the lung damage caused by asthma has already occurred if its onset was during childhood, new problems arise. Adherence to medication is low and many people with persistent symptoms disengage from treatment.⁴⁰ Despite new treatment paradigms, such as combinations of inhaled corticosteroids and long-acting β-adrenoceptor agonists that can be used as needed (anti-inflammatory relievers), many people and clinicians continue to rely on short-acting bronchodilators, and short-course oral corticosteroids for flare-ups. Between 2012 and 2021, nationally representative surveys in Australia found declining levels of self-management by adults with asthma: fewer people regularly used inhaled corticosteroid preventers, poor symptom control was more frequent, and the number of self-reported asthma-related hospitalisations quadrupled. 40 Current treatments can be adapted to individual patient needs, but often fail to meet them. The hospitalisation rate for Australians with asthma is higher than in other OECD countries, and excessive use of systemic corticosteroid therapy adds further harm. 41 Previous advances in asthma management reduced asthma-related mortality, but it is again rising, ¹⁰ and we have not done anything to relieve the possibly rising burden of daily symptoms and exacerbations. We have failed to build on our successes to reduce the increasing day-to-day cost and burden of asthma.

Our mission to CURE asthma by attacking its root causes cannot distract from the continuing and pressing need to translate already available knowledge into better practice. The importance of using available treatments better now cannot be overstated. However, even were we to achieve 100% medication adherence, we estimate that direct asthma medication costs in Australia would exceed \$1 billion each year and would still not eliminate the asthma burden. It is clear that

a substantial shift in the quality and personalisation of care is urgently needed, but no current treatment is truly disease-modifying or curative for most people with asthma, particularly those for whom social determinants of health play a major role. The CURE Asthma mission focuses on fundamentally attacking the underlying mechanisms of disease, and levelling the playing field for all, across all socio-demographic domains.

The significant medical, social, and economic burden of asthma is a strategic opportunity for Australian biomedical research commercialisation, especially as funding agencies increasingly prioritise support for research with the potential for economic impact. The annual value of the global asthma therapeutics market is projected to reach nearly US\$60 billion by 2030,⁴² providing a highly competitive environment in which curative therapies could redefine the standard of care. Precedents in other fields — such as triple-modulator therapy for cystic fibrosis⁴³ (US\$36 billion by 2031⁴⁴), glucagon-like peptide-1 (GLP-1) agonists for metabolic disease⁴⁵ (US\$71 billion by 2032⁴⁶), and immune checkpoint inhibitors for cancer⁴⁷ (US\$150 billion by 2031⁴⁸) indicate that transformative treatments can reshape markets and even influence national economic figures.⁴⁹ These successes have generated intense commercial interest in curative asthma therapies and indicate the enormous opportunity for Australian biomedical research commercialisation.

Medical research has entered a period of immense opportunity in which fundamental research into disease mechanisms, linked with new methods of drug design and precision medicine development, are accelerating rapidly and synergistically, pushed forward by profound advances in machine learning and artificial intelligence.⁵⁰ We are finally cutting through once inextricably tangled Gordian knots of pathobiology and discovering cures in other diseases. Most recently, transformative medicines for β-thalassemia, adenosine deaminase deficiency, and aromatic L-amino acid decarboxylase deficiency have been registered. 51-53 Asthma is not as simple as rare monogenetic diseases. It is heterogenous, polygenetic, and comprises distinct endotypes, but these breakthrough strategies presage the future of medicine, in which we can build upon advances in molecular and computational science to accelerate progress towards cures.

A conceptual shift is already underway, led by advances in treating severe asthma with biological agents; treatment goals are moving from symptom control to sustained on-treatment remission. ^{54,55} This approach will be expanded to include people with mild and moderate disease. Conceptually, ontreatment remission can be seen as a stepping stone to off-treatment cures. The time to act is now.

Are cures scientifically feasible?

Incredible technological advances are enabling us to increase our understanding of disease biology at a molecular level and discover what is driving many of our most complex diseases.

The more knowledge we gain, the better we can predict the clinical success of our candidate drug molecules, accelerating their delivery to get the right treatments to the right patients. *Mene Pangelos, former executive vice-president, AstraZeneca.* ⁵⁶

Recent research findings suggest that curing asthma is scientifically feasible. As asthma comprises multiple distinct endotypes, "cure" will mean a family of distinct solutions rather than a single effective intervention. Long term findings of Australian and overseas cohort studies indicate that some people with asthma can experience spontaneous lasting remission. ⁵⁷ Asthma is an acquired condition, and complete spontaneous remission and on-treatment remission ⁵⁷ can now be achieved in some patients, which also indicates that asthma can be cured. Defining the molecular basis for the clinical features of lasting off-treatment remission is one of the keys to developing curative strategies.

In an Australian registry data-based assessment of the effectiveness of biological therapies, 23–29% of adults with asthma achieved clinical remission (defined as no exacerbations and no oral corticosteroid use) and 19-25% achieved both clinical remission and stable lung function.⁵⁸ Given that so many people receiving such therapies achieve on-treatment remission, interest in identifying "super-responders" (those for whom the therapy is profoundly effective) is growing, supporting proposals to define remission as a formal treatment goal.⁵⁹ Further, a placebo-controlled trial of another Australian-led treatment innovation, macrolide therapy for severe asthma (the AMAZES trial), found that clinical remission was achieved in as many of 50% of intervention group participants with eosinophilic or non-eosinophilic asthma. These findings have changed care for people with asthma around the world.61

While our goal of cures for asthma is ambitious, the scientific progress described in the articles in this supplement supports their feasibility. Genome-wide association studies have identified genetic variants associated with complete remission, including single nucleotide polymorphisms (SNPs) in genes related to tissue repair, protein folding, and inflammation. Epigenetic studies have found persistent molecular scars, altered DNA methylation patterns related to unresolved airway injury. These findings help distinguish between pathogenic processes that resolve (as in spontaneous remission) or persist (as in asthma). Combined with insights from immunomodulation trials, 65,66 the growth in molecular information is clearing the path to transformative, curative therapies.

Building on decades of success and investment: the unique advantages of Australia

The CURE Asthma initiative is uniquely positioned to drive transformative progress by building on decades of leading clinical research, longitudinal cohort epidemiology, and fundamental basic and discovery research in Australia. These resources are the legacy of sustained national funding of asthma-related research,

including \$348 million from the National Health and Medical Research Council for lung disease (2000–2022) and \$283.8 million from the Medical Research Future Fund for respiratory health, although only a small fraction (\$11.3 million; eight of 151 grants) was specifically for asthma research.¹⁷

A major strength of the CURE Asthma initiative is its access to eleven of the most valuable Australian longitudinal cohort studies, encompassing more than 75 000 participants for whom comprehensive phenotyping, archived biological samples, and longitudinal lung function data are available, coupled with the machine learning-capable CURE-Asthma Data Integration Research Engine (CURE-ADIRE). The included cohorts span more than 60 years across the entire lifespan, and the dataset includes familybased data from parents, children, and siblings, as well as a limited amount of information for First Nations participants in some studies. The ongoing cohort studies are unparalleled in both scale and comprehensiveness, making it a national resource of international significance. We estimate that replicating these cohort studies would today cost more than \$1 billion. For context and comparison, the three-year international NOVELTY observational study of real world airway disease (12000 participants, limited biological sample collection, and no lung function data, but including smaller sub-studies)⁶⁷ is estimated to have cost more than AU\$160 million (NCT02760329) 68 and the ten-year United States COPDGene⁶⁹ (genetic epidemiology of COPD) program (about 10000 patients) has cost about AU\$118 million (two National Institutes of Health U01 investigator-initiated early stage clinical studies [2007–2011] and two R01 research project grants [2012-2016]).

By combining our exceptional national resources with cutting edge advances in molecular science, computational biology, and innovative methods, including digital twin technologies that more rapidly link discovery with clinical trials, ⁵⁰ the CURE Asthma initiative is an unprecedented opportunity for accelerating the translation of research findings and bringing curative therapies within reach. We are at the nexus of compelling unmet patient and medical need, technical feasibility, market appetite, and an advantageous national strategic position. We stand at the beginning of the next bioscience revolution and call on all who care about people with asthma — children and adults with mild to severe disease — to support our transformative vision.

The articles in this supplement outline current knowledge about the nature of asthma and a realistic research strategy for finding transformative new therapies. Taken together, they comprise the rationale and the roadmap supporting our call for large, sustained, and focused CURE Asthma funding over the coming decade.

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