Lung transplantation in Australia, 1986–2018: more than 30 years in the making

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Summary

- Lung transplantation in Australia is 32 years old in 2018. From its early infancy in 1986, it continues to evolve and is internationally recognised as demonstrating world's best practices in organ donation, utilisation and transplantation procedures.
- Over the past decade, transplant numbers have increased substantially due to innovations in donor procurement, such as donation after circulatory death, the use of ex vivo lung perfusion, extended criteria and organ utilisation, with more than 200 lung transplants undertaken in Australia annually. Parallel to this, lung transplant outcomes have continued to improve.
- While the management of lung transplant recipients is heavily dependent on a tertiary care paradigm, this model is well developed and has been extremely successful, with Australian outcomes exceeding those of the International Society for Heart and Lung Transplantation Registry at all time points.

It has been more than 50 years since James Hardy performed the first cadaveric human lung transplant procedure in Mississippi in 1963.[1] While the recipient of this single lung transplant survived only 18 days, the achievement demonstrated the technical feasibility of lung transplantation.

Despite this early surgical success, subsequent procedures over the following decades demonstrated poor outcomes due to early bronchial anastomotic complications and the lack of immunosuppressive agents available to avert rejection. The discovery of cyclosporin in 1976[2] revolutionised solid organ transplantation and heralded the progression towards longer term survival. In 1981, the first successful heart–lung transplant was undertaken for pulmonary arterial hypertension.[3] This was quickly followed by the first single lung transplant for idiopathic pulmonary fibrosis in 1983[4] and bilateral lung transplant for chronic obstructive pulmonary disease in 1986.[5] By this point, evolution in surgical techniques and improvements in immunosuppression meant that longer term success could be achieved, with the first bilateral lung transplant recipient surviving for 15 years. The 1990s saw the development of Australian lung transplant programs, with the first heart–lung transplant performed in 1986 and the first isolated lung transplant in 1990 at St Vincent's Hospital, Sydney.[6]

Over the past 30 years, lung transplant techniques and immunosuppression regimens have evolved, improving short and long term outcomes and making lung transplantation a viable option for those with end-stage lung disease. More than 60 000 adult lung transplants have been performed to date worldwide. In 2015, 4122 transplants were reported to the International Society for Heart and Lung Transplantation (ISHLT) Registry,[7] with 200 (about 5%) lung transplants performed in Australia in the same year.[8]

Australia currently has four adult lung transplant programs: Brisbane, Sydney, Melbourne and Perth. Additionally, Adelaide and Hobart run satellite services, providing long term post-transplant care beyond the 3-month mark. A nationally funded paediatric lung and heart–lung transplant program based in Melbourne is run conjointly by the Royal Children's Hospital and the Alfred Hospital, providing lung transplantation services to all Australian children aged 4–16 years.

We undertook a literature review of international and local publications. International and Australian registry data were used, with a special focus on Australian data.

Changes in donation patterns and transplant numbers

Despite increasing transplant numbers, lung transplantation remains limited by donor supply. Historically, waitlist mortality has been high, with 15–20% of lung transplant candidates dying while on a waitlist. In 2008, a federal government initiative led to the development of the national Organ and Tissue Authority with the aim of implementing world's best practice in Australia for organ and tissue donation.[9] This translated into increased donation rates nationwide, climbing from 11.4 per million population in 2009 to 20.8 per million population in 2016.[10] While increasing donor numbers led to an increase in transplants, Australia's lung transplant centres additionally embraced innovative strategies and techniques to maximise the number and quality of potentially transplantable lungs[11,12] and, as a result, Australia has one of the world's highest lung transplantation rates per million population[13] (Box 1).

The two available donation pathways are donation after brain death (DBD) and donation after circulatory death (DCD). Brain death occurs in the setting of severe brain injury, and its diagnosis requires evidence of an acute brain pathology either clinically or on neuroimaging consistent with the irreversible loss of neurological function, an unresponsive coma and the absence of brainstem reflexes and respiratory centre functions.[14] Historically, the most common conditions leading to brain death were traumatic brain injury and subarachnoid haemorrhage.[15]

While DBD remains well understood, the DCD pathway has developed over the past decade as an alternative path to donation in non-brain-dead individuals for whom ongoing treatment is deemed futile. In this setting, potential donors are individuals with illnesses or injuries incompatible with survival without ongoing intensive care or ventilatory support; for example, severe irreversible brain injuries (not meeting the criteria for brain death), or severe cardiac or respiratory failure.[14]

The Maastricht classification for DCD[14] (Box 2) describes potential situations that could lead to DCD transplants. In Australia and New Zealand, lung transplantation has most commonly and successfully used Maastricht category III (awaiting cardiac arrest), with evidence showing excellent outcomes that are at least equivalent if not superior to DBD transplants.[16,17]

Australian lung transplant programs have been early adopters of the use of DCD organs, leading to a significant increase in

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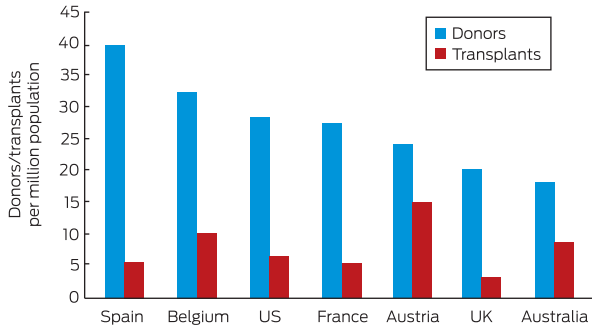
1 Australian lung transplant activity per million population in 2015: total donors compared with number of transplants, by selected countries*



World rank	Spain	Belgium	US	France	Austria	UK	Australia
Donors per million population	1	3	6	7	10	14	18
Lung transplants per million population	11	2	6	12	1	20	3
Proportion utilised	14%	31%	22%	19%	62%	15%	44%

* Data adapted from International Society for Heart and Lung Transplantation Registry report[7] and ANZOD Registry 2016 annual report.[13] Donors per million population refer to organ donors referred for consideration of transplantation. Transplantation rates are affected by the donors per million and by the utilisation rate. Despite being ranked overall as 18th in the world in terms of donor number per million population, Australia ranks third in terms of lung transplants per million population, owing to a high donor utilisation rate of 44%.[8] ◆

transplant numbers, with more than 300 DCD lung transplants performed since 2006. This represents the world's largest national cohort and accounts for 23% of all Australian lung transplants performed[16,17] (Box 3). The National Donation-After-Determination-of-Cardiac-Death Lung Transplant Collaborative has allowed the nationwide coordination and development of protocols and facilitated audit. DCD lung transplantation will likely further expand into the other categories, eventually comprising an even greater proportion of Australian lung transplants.[17]

Guidelines for referral for transplant

Local and international guidelines describing recipient selection criteria have been developed by the Transplantation Society of Australia and New Zealand[18] and the ISHLT.[19] However, each transplant centre interprets these guidelines according to their own ethos, experience and expertise leading to geographical differences in practice. Absolute and relative contraindications for lung transplantation change over time. Current considerations are detailed in Box 4. Of note, there have been considerable changes in some key areas.

Age

Although advanced age itself is not an absolute contraindication, candidates > 65 years are only considered suitable for evaluation if there are minimal comorbidities, a paucity of relative contraindications and the ability to demonstrate reasonable physical reserve. Frailty is associated with poorer outcomes both before and after transplantation, influencing suitability.[20,21]

Malignancy

The majority of invasive malignancies require 5 years of sustained disease-free remission before consideration for lung transplantation. However, the prospect for patients with active prostate adenocarcinoma has changed significantly in recent years. Given that the predicted life expectancy of those with localised disease exceeds that of lung transplantation[22] and emerging evidence suggesting that immunosuppression does not accelerate progression,[23] this specific malignancy is no longer considered an absolute contraindication.

2 Maastricht classification for donors after circulatory death[14]

Classification	Grade	Description
Uncontrolled	I	Dead in the out-of-hospital setting
	II	Unsuccessful resuscitation
Controlled	III	Awaiting cardiac arrest
	IV	Cardiac arrest while brain dead

Social and psychological factors

Despite challenges in the assessment and management of current or historical non-adherence (including the impact of psychological and psychiatric conditions), these factors remain relative contraindications owing to their association with poorer outcomes.[24-26]

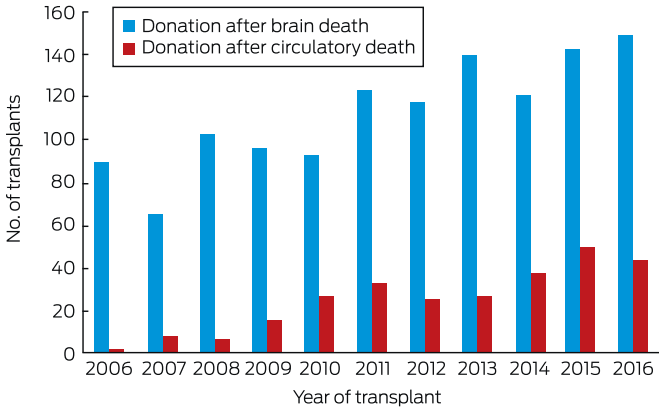
Indications for transplant

In Australia and internationally, the most common indication for lung transplantation has been chronic obstructive pulmonary disease. As treatments evolve, transplants for cystic fibrosis make up less of the population while interstitial lung disease is becoming an increasingly common indication.[7,8] The majority of lung transplants performed today are bilateral lung transplants (Box 5), with 203 performed in Australia in 2016, compared with seven single lung and seven heart–lung transplants[8]

Timing of referral

A timely referral for consideration for lung transplantation is paramount to a successful outcome. Referral simply implies that a patient has met the minimum clinical characteristics that might warrant transplant consideration. Early referral allows maximum flexibility in performing the formal evaluation and in making the second, more important step — activation on the waiting list. Despite limited data to guide us, the principles of candidacy consideration as per ISHLT guidelines are as follows:[19]

3 Lung transplant activity in Australia, 2006–2016: donation after brain death compared with donation after circulatory death[8]



4 Relative and absolute contraindications to lung transplant*

- Untreatable other organ dysfunction
  - for example, heart, liver, kidney or brain, unless combined organ transplantation can be performed
- Malignancy
  - disease-free interval will be dependent on type of malignancy and predicted risk of recurrence after lung transplant; a 2-year disease-free interval may be reasonable in treated non-melanoma localised skin cancer while a 5-year disease-free interval will be required in many other cases
  - there will be some patients in whom the risk of recurrence may remain too high to proceed with lung transplantation even after a 5-year disease-free interval
- Non-adherence
- Morbid obesity
- Substance misuse
  - including but not limited to alcohol, tobacco, marijuana or other illicit substances
  - convincing evidence of risk reduction behaviours, and evidence of abstinence using serial blood and urine testing may be required
- Age
  - assessment of age and physiological reserve required for all recipients
- Poor social supports
  - absence of an adequate or reliable social support system
- Poor rehabilitation potential

* Adapted from Weill et al.[19] ◆

- high (> 50%) risk of death from lung disease within 2 years;
- high (> 80%) likelihood of surviving at least 90 days after lung transplantation; and
- high (> 80%) likelihood of surviving at least 5 years from a general medical and comorbidity perspective provided there is adequate graft function.

Certain criteria that may suggest appropriateness of referral are listed in Box 6. Of particular note, early referral of patients with interstitial lung disease is essential, before severe loss of conditioning and function. The trajectory of these conditions is often tenuous and unpredictable, where a late referral may deem the patient unsuitable for transplantation.

Paediatric lung transplantation

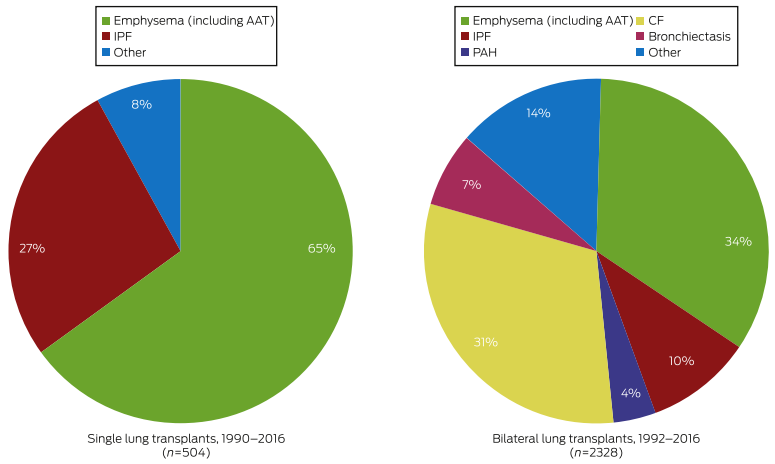
In children, advanced lung disease is rare and therefore the need for lung transplantation is uncommon. Globally, no more than 100 paediatric lung transplants are performed each year,[27] and in Australia this equates to an annual incidence of three to six transplants. Reflecting the low volume and complex nature of the procedure, paediatric heart–lung and lung transplantation is performed at a single centre under the Nationally Funded Centre Program.

Indications for transplantation in children differ from those in adults, with the most common indications being cystic fibrosis and pulmonary arterial hypertension.[27] Most children receive bilateral lung transplants, with heart–lung transplants reserved for smaller children (typically < 20 kg) with pulmonary hypertension in whom the enlarged heart restricts space within the chest cavity.

Reflecting their small size and a relative paucity of paediatric organ donors, it is recognised that children are exposed to higher waitlist mortality than adults. To circumvent this, a number of strategies to expedite access to transplantation have been adopted, including consideration of the use of extracorporeal membrane oxygenation as a bridge to transplant,[28] use of DCD or extended criteria donor lungs,[16] and lobar transplants from an over-sized adult donor.[29]

Outcomes in children are equivalent to those in adults, although non-adherence, particularly through the adolescent years, is a major contributor to early mortality[30] and may be a barrier to consideration of re-transplantation. Additionally, the risk of post-transplant lymphoproliferative disorder is significant in children, many of whom have never been exposed to Epstein–Barr virus (EBV). Such EBV-naive patients who receive EBV-positive organs have an up to 50% risk of developing post-transplant lymphoproliferative disorder necessitating lifelong anti-viral prophylaxis.[31]

5 Lung transplant types and indications in Australia



AAT = α-1 antitrypsin deficiency; CF = cystic fibrosis; IPF = idiopathic pulmonary fibrosis; PAH = pulmonary arterial hypertension. The majority of lung transplants currently undertaken are bilateral. However, single lung transplants continue to be undertaken predominantly for emphysema and interstitial lung disease. ◆

Donor evaluation and management

Careful evaluation of donor lungs is required before consideration for lung transplantation, irrespective of the pathway of donation (DCD *v* DBD). A thorough history is acquired from the donor's relatives or close friends, assessing for a history of smoking, high risk behaviours, malignancy and lung disease. Chest x-rays are performed routinely for all potential donors, while computerised tomography is reserved for those with concerning features on history or an abnormal x-ray.

Ideally, key requirements for lung donation include a PaO_2/FiO_2 ratio > 300, normal chest imaging and an absence of significant secretions or aspiration.[32,33] In reality, lungs that are believed to be inherently acceptable (both structurally and functionally), but are acutely impaired will often become suitable over time if managed appropriately (for example, through the use of ventilatory strategies, diuretics and other recruitment manoeuvres).[34-36]

6 Referral criteria*

Condition	Criteria
Chronic obstructive pulmonary disease	Progressive disease despite maximal treatment including medication Pulmonary rehabilitation and oxygen therapy FEV_1 < 25% BODE score, 5–6 $PaCO_2$ > 50 mmHg and/or PaO_2 < 60 mmHg Pulmonary hypertension
Interstitial lung disease	Histopathological or radiographic evidence of usual interstitial pneumonia or fibrotic non-specific interstitial pneumonitis Abnormal lung function: FVC < 80%; DLCO < 40% Any dyspnoea or functional limitation attributable to disease Any oxygen requirement Connective tissue disease associated with interstitial lung disease: failure to improve after clinically indicated trial of therapy
Cystic fibrosis	FEV_1 < 30% or rapid decline despite optimal therapy Virulent infection (non-tuberculous mycobacteria or *Burkholderia cepacia* complex) Pulmonary hypertension Clinical decline characterised by: • increasing antibiotic resistance and poor clinical recovery from exacerbations • pneumothorax • life-threatening haemoptysis despite embolisation • worsening nutritional status despite supplementation
Pulmonary arterial hypertension	New York Heart Association class 3 or 4 despite escalation of treatment Rapidly progressive disease Use of parenteral targeted therapy regardless of symptoms Pulmonary veno-occlusive disease or pulmonary capillary haemangiomatosis

BODE = body mass index, airflow obstruction, dyspnoea, and exercise; DLCO = diffusing capacity of the lungs for carbon monoxide;.FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; * Adapted from Weill et al.[19] ◆

Fibre optic bronchoscopy is routinely performed on the donor, not only to visually inspect the major airway, but also to collect a bronchial washing sample to help guide the recipient's antimicrobial regimen. In order to optimise gas exchange, enhance alveolar recruitment and protect the lungs before procurement, the intensive care unit will instigate targeted ventilation strategies which have been shown to improve organ utilisation rates.[35-39] The time from acceptance of donor organs to procurement may be many hours or even days, stressing the importance of close monitoring and regular assessment.

Ex vivo lung perfusion (EVLP) of donor lungs is emerging as an Australian reality. EVLP describes a system of evaluation and potential therapeutic manipulation of explanted donor lungs (either DBD or DCD) before implantation into a potential recipient. It enables the reconditioning and reassessment of donor organs not found immediately suitable. Typically, such lungs undergo 4–6 hours of EVLP reconditioning, with 60–90% subsequently found suitable for transplantation.[40,41] Internationally, the clinical outcomes of transplantation using lungs assessed via EVLP have been equivalent to those of conventional non-EVLP donors;[40] however, EVLP is currently not routinely used by all Australian centres.

Donor and recipient compatibility

In Australia, donor allocation remains the jurisdiction of individual transplant units, to which potential donors are referred based on geographical allocation. In general, donor-recipient matching is determined by ABO blood group and size compatibility, absence of positive T cell crossmatch, clinical urgency, logistics, potential recipient long term outcome and recipient waitlist time. Identical ABO blood group matches are preferred and predominantly used.

Size matching of donor to recipient is usually based on donor and recipient height, plus estimates of lung volumes from chest x-rays.[41,42] While the optimal fit remains unknown, a close match is preferred and leads to good outcomes. Importantly, the recipient's underlying disease will influence the size match; emphysematous recipients with a larger thoracic cavity are able to receive larger donors and are transplanted more readily, compared with those with interstitial lung disease and a smaller thoracic cavity.

A complement-dependent cytotoxicity assay in conjunction with a solid phase assay is performed prospectively on all potential transplant recipients to assess for donor-specific antibodies. Sensitisation to donor-specific antibodies is avoided and remains a major impediment to transplantation with implications for organ access and post-transplant outcomes. There is clear evidence that sensitising events such as blood transfusions, pregnancies and prior transplantation can result in the formation of human leucocyte antibodies, leading to difficulties in finding suitable immunologically matched organs and increasing a potential recipient's wait time.

The increase in donor numbers and evolution of retrieval techniques has led to a significant reduction in waitlist time and mortality in Australia. Median wait time is 116 days and waitlist mortality in some centres as low as 5%.[8] Despite this, a variation in wait time exists in those who are sensitised and between the blood groups, with AB blood group recipients waiting on average 51 days compared with 180 days for blood group O and 221 days for blood group B.[8] Despite careful waitlist management, certain individuals are inherently harder to find suitable organs for and transplant in a timely fashion. For this reason, blood group O patients, multiparous women who are highly sensitised, and patients with interstitial lung disease and small thoracic cavities should be referred early.

General post-operative management

The majority of transplant recipients receive a triple immunosuppression regimen of a calcineurin inhibitor, azathioprine or mycophenolate, and prednisolone.[7] Triple immunosuppression remains lifelong, with no convincing evidence for prednisolone-free regimens.[7,43] Immunosuppression doses are reduced over the first year as the risk of acute rejection declines. Other changes over time are likely to reflect an individual patient's complications and comorbidities. Regular surveillance occurs with spirometry and bronchoscopy to examine for rejection and infection.

Infection prophylaxis is used routinely and includes peri-transplant intravenous empiric broad-spectrum antibiotics as well as lifelong low dose co-trimoxazole for pneumocystis jiroveci pneumonia prophylaxis. Cytomegalovirus (CMV) historically caused significant morbidity and mortality in lung transplant recipients. The evolution of ganciclovir and later valganciclovir allowed the provision of effective CMV prophylaxis, with extended prophylaxis utilised in most centres[44] because shorter course regimens (3 months) resulted in a high incidence of late CMV reactivation associated with chronic lung allograft dysfunction.[45] A recent Australian study examined the use of a commercially available CMV test to guide duration of prophylaxis, reducing late CMV reactivation and allowing the personalisation of CMV prophylaxis for individual patients.[46]

Post-transplant rehabilitation occurs in the acute setting in most Australian units, and has been shown to improve functional exercise capacity, muscle strength[47] and bone mineral density.[48]

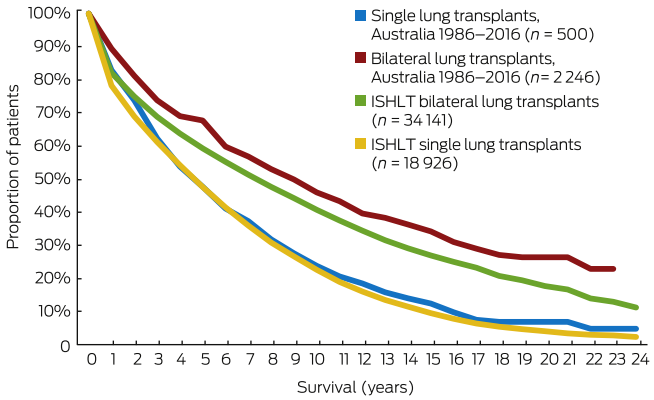
The management of lung transplant recipients is heavily dependent on a tertiary care model. Regular review at a transplant centre to monitor immunosuppression levels, spirometry and short and long term complications allows the fine tuning of treatments and early intervention in the event of infection or lung function decline. This model is well developed and has been extremely successful, with Australian outcomes exceeding those of the ISHLT Registry at all time points[7,8] (Box 7).

Post-transplant outcomes

Australian units have experienced a 50% increase in lung transplant activity since 2006, from a historical average of 100 lung transplants per year to more than 200 in 2015.[8] In conjunction, long term survival has continued to improve; current reported survival of bilateral lung transplant recipients at 1, 3 and 5 years is 90%, 74% and 68%, respectively,[8] which exceeds international survival rates of 82%, 69% and 59%, respectively (Box 7).

The purpose of lung transplantation is to improve quality of life and extend survival in patients with end-stage lung disease. Lung function tends to improve over time, with most bilateral lung transplant recipients normalising their spirometric indices.[49] Return to normal function, education and employment roles remains the goal, with the majority of patients reporting significant improvements in quality of life and an unencumbered lifestyle.

7 Lung transplant survival: Australian data compared with International Society for Heart Lung Transplantation Registry (ISHLTR) data*



* Data sourced from Chambers et al[7] and ANZCOTR 2016 annual report.[8] ◆

International data suggest that more than 80% of patients report no activity limitation and 30% of 5-year survivors are working at least part-time.[7]

Overall, long term outcomes are limited by chronic lung allograft dysfunction. Although traditionally regarded as synonymous with bronchiolitis obliterans syndrome demonstrated by an obstructive decline in spirometry, other phenotypes are increasingly recognised, with a restrictive form of chronic lung allograft dysfunction — restrictive allograft syndrome — newly described.[50] Chronic lung allograft dysfunction (manifest by bronchiolitis obliterans syndrome or restrictive allograft syndrome) is the leading cause of death after the first year, with an incidence of > 50% at 5 years. Infectious complications account for 35% of deaths in the first year, and remain a significant cause of mortality in later times, with 20% of deaths after 1 year due to pneumonia, respiratory viruses, CMV or fungi. While malignancy is rare early on, it increases with time. The most common malignancy is non-melanomatous skin cancer followed by post-transplant lymphoproliferative disorder.[7,8]

Conclusion

Lung transplantation in Australia continues to grow and evolve, and is internationally recognised as demonstrating world's best practices in organ donation, utilisation and transplantation procedures. The success of Australian lung transplant programs is evidenced by their excellent outcomes, and driven by a commitment not only to outstanding clinical care but also to ongoing research endeavours and collaborations.

Competing interests: No relevant disclosures

Provenance: Commissioned; externally peer reviewed. ■

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