



Australian Government

Department of Health and Aged Care

Recommendations on Adult Haemopoietic Progenitor Cell Donor Recruitment Reform

HPC Sector Clinical Advisory Group

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Contents

Introduction	2
International network of Registries	2
Current HPC donor recruitment and testing in Australia	3
The National HPC Framework.....	4
Haemopoietic Progenitor Cell (HPC) Sector Clinical Advisory Group	4
Membership.....	4
Reform of unrelated adult HPC donor recruitment in Australia: Recommendations	6
Key messages	6
Proposed timelines for Implementation.....	9
Immediate actions	9
Short-term actions (within next 6 to 12 months).....	10
Long-term actions (12 months onwards).....	12
Background	14
Current national HPC registry size	15
Current Australian HPC recruitment strategy.....	15
Standards for testing at HPC recruitment – current practice	19
Australian regulation and accreditation of HPC donor recruitment testing.....	20
Potential Future National HPC Donor Recruitment Strategy	22
Standards for testing of samples at HPC donor recruitment – future practice.....	22
Proposed changes to the HPC donor recruitment target and recruitment method	26
Appendix 1:	28
Testing performed on recruitment samples by international HPC donor registries	28

Introduction

International network of Registries

There are currently 40,908,762 adult donors and cord blood units listed in the World Marrow Donor Association (WMDA) database¹ encompassing cord blood banks and (adult) donor registries across the globe. The Australian haemopoietic progenitor cell (HPC) registry is part of this worldwide network of HPC donor registries, where overseas donors provide HPCs for Australian patients, and vice versa. The WMDA sets the minimum international standards for activities involved in the provision of HPCs for transplant with international registries requiring accreditation against these standards.

Registries in each country determine their own donor recruitment strategies and testing of samples in line with the WMDA standards and their own national accreditation and regulatory frameworks. This includes the recruitment of adult volunteers to become a HPC donor through the provision of a blood or buccal swab sample. In Australia the national registry is managed by the Australian Bone Marrow Donor Registry (ABMDR)². The ABMDR is a member of, and accredited by, the WMDA. The ABMDR, through its Scientific and Expert Advisory Committee (SEAC), consider the WMDA standards³ and set minimum Australian donor testing requirements at recruitment.

Consistent with worldwide practice, the majority of HPCs used in Australia are now derived from blood rather than bone marrow. Similarly, a small proportion (<10% per year) of all stem cell transplants in Australia are performed using HPCs from banked cord blood units (CBUs)⁴. The choice of HPC source for a transplant made by the clinician is dependent on the available therapeutic options, patient age, disease characteristics and the availability of a suitably matched adult donor or banked CBU.

The selection by a clinician of the most appropriate HPC donor for their patient is primarily driven by patient's tissue-type (also known as the human leucocyte antigen (HLA) type) and availability of an appropriately matched donor, with the outcome of a HPC transplant being highly dependent on the degree of HLA matching⁵. The search for a donor for an Australian recipient is done sequentially with the identification and testing of any potential family/related donors, followed by searching for an unrelated Australian donor (ABMDR registrants). If a suitable domestic donor cannot be identified, then a search of overseas registries is performed. This may result in HPCs being sourced from overseas rather than from the Australian registry. This phenomenon is commonplace across the globe, as no single country or geographical region is self-sufficient for its own adult donor HPC or CBU needs¹.

In 2022, 80% of all unrelated HPC transplants performed in Australia used HPCs from an overseas donor⁶. Transplants utilising overseas donor HPCs are vulnerable to the timely availability of the overseas donor, tissue collection and processing, and variations in commercial air transport routes.

¹ WMDA data sourced on 3 April 2023 from: <https://wmda.info/>

² For the purposes of this report, the national adult donor HPC registry (national registry) is used to describe the donor registry and ABMDR is used to describe the organisation contracted to manage the services of the national registry.

³ WMDA International Standards: Unrelated Hematopoietic Stem Cell Donor Registries accessed via https://wmda.info/wp-content/uploads/2021/01/WMDA-2020-Standards_AM1_Jan2021-1.pdf

⁴ Australian Bone Marrow Transplant Recipient Registry Annual Data Summary 2015- 2020 accessed via <https://www.abmtrr.org/index.php/annual-data-summary/>

⁵ Lee *et al*, 2007 Blood. Accessed from:

<https://www.sciencedirect.com/science/article/pii/S0006497120529091#bib21>

⁶ ABMDR 2022 Annual Registry Report

The COVID-19 pandemic resulted in donor cells being processed and cryopreserved prior to shipment to the Australian transplant centre, which added not only logistical complexity to the transplant process but increased the cost of these donor cells to the Australian healthcare system. Although export revenue for the use of an adult donor HPC to international patients is received by ABMDR, there is a net cost imbalance due to the high percentage of Australian patients currently requiring more costly donor cells from overseas.

Current HPC donor recruitment and testing in Australia

In the absence of a current formalised national plan for HPC recruitment and testing, the ABMDR and the Australian Red Cross Lifeblood (Lifeblood) have undertaken HPC recruitment activities in parallel. There is also notable and substantial engagement of highly motivated patient representative groups advocating for changes to current donor recruitment on behalf of individual patients for whom HPC donors may be immediately difficult to identify.

Lifeblood is contracted to recruit individuals to the national registry when they present to a Lifeblood centre as a blood donor. Lifeblood is funded for the testing of all blood donor recruitment, but HPC recruitment and HLA typing is not covered by the Deed of Agreement between Lifeblood and the National Blood Authority. HPC donor recruitment and HLA testing is funded via separate agreements with each state or territory. This is further complicated with two states contracting Lifeblood for only HPC donor recruitment and contracting the HLA testing within their own state pathology entities.

Most blood donors do not currently undergo HLA typing, only those who elect to become platelet donors undergo such testing. As with HPC registrants, there is a limited pool of domestic platelet donors, particularly those with rare HLA or human platelet antigen (HPA) expression. This leads to increased pressure on identifying appropriate platelet donors, and those individuals to be called upon more frequently to repeatedly provide platelet donations. The register of platelet donors is held separately to HPC donors on the national registry.

Currently, there are very few Australian testing providers accredited to perform HLA testing using buccal swab samples. There are no Australian providers of buccal swab-based testing for either molecular blood group (ABO and Rhesus⁷ (Rh)D testing), or cytomegalovirus (CMV) immunoglobulin (Ig) testing, which are mandated for HPC donor recruitment.

The ABMDR has performed two recruitment pilot programs (Strength to Give 1 and 2) that used buccal swab-based samples. These samples were sent to overseas laboratories (Histogenetics and/or DKMS) during Strength to Give 1 (STG1: 2019-2020). During Strength to Give 2 (STG2: 2020-2021) HLA typing was performed by PathWest with ABO and Rh blood group and CMV testing performed overseas.

⁷ Throughout this report Rhesus (Rh) systems or Rh blood group refers to testing for the Rh D antigen. It should be noted that the Universal Blood Donor Testing (UBDT) array is able to detect all Rh antigens.

The National HPC Framework

In 2021, all Governments agreed upon the implementation of the National HPC Framework (Framework)⁸. The Framework describes five long-term strategic objectives for the development of the HPC sector in Australia. These are to:

1. Facilitate safe, standardised, high quality clinical HPC services for all Australians.
2. Facilitate equitable access to life saving HPC transplantation for all Australian patients, ensuring the needs of vulnerable groups are met.
3. Ensure HPCs are supplied through efficient, effective, appropriate service delivery and that the supply addresses clinical and patient needs.
4. Reduce reliance on internationally sourced HPCs for transplantation, through improvements to tissue typing and improved donor recruitment that is evidence-based (i.e. based on true clinical demand with consideration of emerging trends).
5. Enable appropriate development and implementation of national and state and territory strategies to support governance and operations that enhance coordination across the sector.

In parallel to the consideration of adult donor recruitment reform in Australia, the cord blood sector is also being reviewed by the Jurisdictional HPC Committee (JHPCC) which oversees HPC policy and its funding in Australia.

This report provides the recommendations from the HPC Sector Clinical Advisory Group on unrelated adult donor HPC recruitment reform in Australia.

Haemopoietic Progenitor Cell (HPC) Sector Clinical Advisory Group

The Haemopoietic Progenitor Cell (HPC) Sector Clinical Advisory Group (Advisory Group) was established by the Department of Health and Aged Care in 2022 to provide advice to the Jurisdictional HPC Committee to support the implementation of the [National HPC Framework](#).

Membership

The Advisory Group currently comprises of 12 members with expertise in clinical haematology including HPC transplantation, scientific expertise in histocompatibility HLA typing, as well as experts in Australian laboratory accreditation and regulations (Table 1).

⁸ [National HPC Framework, https://www.health.gov.au/our-work/haemopoietic-progenitor-cell-framework-and-programs?language=und](https://www.health.gov.au/our-work/haemopoietic-progenitor-cell-framework-and-programs?language=und), published November 2021

Table 1: Expertise and Affiliation of Advisory Group Members

Name of Member	Nature of Participation	Affiliation
Dr Neil Everest (Chair)	Commonwealth Medical Adviser to the JHPCC	Senior Medical Adviser, Technology Assessment and Access Division, Department of Health and Aged Care (DoHAC)
Professor Robert Carroll	Clinical Nephrologist & Histocompatibility Expert	Senior Nephrologist, South Australia Health, SA Immunogenetics Laboratory Manager, Lifeblood Australian Red Cross Blood Service
Professor Ian Kerridge	Clinical Haematologist & Bioethicist	Staff Haematologist and Bone Marrow Transplant Physician, Royal North Shore Hospital, NSW Prof of Bioethics and Medicine, University of Sydney, NSW
Dr Richard Mitchell	Clinical Haematologist - Paediatric HPC transplant	Acting Director, Kids Cancer Centre, Sydney Children's Hospital, NSW Director of Transplant & Cellular Therapies Unit, Kids Cancer Centre, Sydney Children's Hospital, NSW
Associate Professor Anna Johnston	Clinical Haematologist	Head of Clinical Haematology and Bone Marrow Transplant, Royal Hobart Hospital, TAS Director, State-wide Bone Marrow Transplant Service, TAS
Dr Duncan Purtill	Clinical Haematologist	Clinical Haematologist and Director of the Bone Marrow Transplant Program, Fiona Stanley Hospital, WA Medical Director, Bone Marrow Transplant Laboratory, PathWest Laboratory Medicine, WA
Dr Beverley Rowbotham	Clinical Haematologist	Consultant Haematologist, Sullivan Nicolaides Pathology, QLD Chair, National Pathology Accreditation Advisory Council, DoHAC
Professor Erica Wood	Clinical Haematologist	Consultant Haematologist, Monash Health, VIC Prof and Head, Transfusion Research Unit, Monash University, VIC
Associate Professor David Yeung	Clinical Haematologist	Head of Haematology, Royal Adelaide and The Queen Elizabeth Hospitals, SA Consultant Haematologist, Royal Adelaide Hospital and South Australia Pathology, SA
Ms Natalie Clark Reynolds	Consumer Advocate	Consumer Representative
Ms Wendy Harris	NATA representative	Lead Accreditation Specialist, National Association of Testing Authorities (NATA)
Ms Fiona McCormack	TGA representative	Principal Technical Advisor, Medical Devices Authorisation Branch, Therapeutic Goods Administration (TGA), DoHAC

Reform of unrelated adult HPC donor recruitment in Australia: Recommendations

Key messages

- The clinical demand for unrelated HPC donors for Australian transplant recipients with blood cancer or severe inherited conditions is mismatched to the level of recruitment of potential HPC donors in Australia compared to other countries. This has resulted in a significant reliance on overseas donors for Australian patients.
- The size of the national registry and pool of optimal HPC donors, currently categorised as being aged 18-35 years, is declining and will continue to decline without substantial changes to the current recruitment targets and testing strategy.
- The HPC donor recruitment target needs to be increased to grow the proportion of clinically preferred donors to be comparable with the mid-range of recruitment seen in similar countries.
 - HPC donor recruitment targets should be revised to collectively achieve 100,000 to 150,000 new recruits to the national registry over a five-year period (25,000 to 40,000 per year).
 - Recruitment should preference populations currently under-represented:
 - (i) according to self-reported ancestry; and
 - (ii) those populations associated with rare HLA subtypes; and
 - (iii) those individuals of mixed ancestry.
- Widening the age-range eligibility from 18-35 years to 18-40 years will assist in reaching the increased HPC donor recruitment targets.
- Whilst male HPC recruits aged 18-40 years are preferred, recruitment should not exclude female volunteers as nulligravida⁹ females are comparable to males as HPC donors¹⁰.
- Implementing buccal swab-based testing alongside current blood sample-based recruitment will increase accessibility of recruitment to more Australians and increase the number of donors recruited to the national registry.
- Current blood-based HLA typing is performed in Australian laboratories at a higher resolution than set by the ABMDR. HLA typing of HPC recruitment samples in Australia should continue at a resolution commensurate with current practice using high-throughput next generation sequencing (NGS). However, it is noted that currently employed NGS based HLA typing is a greater cost.
- Testing of ABO and Rh blood group, plus CMV IgG status should continue to be performed for initial HPC donor recruitment. However, this should not prevent Australian laboratories from performing buccal swab-based HLA typing and blood-based molecular ABO and Rh blood group and CMV IgG testing, whilst comprehensive buccal swab-based ABO and Rh blood group and CMV IgG detection is undergoing validation and subsequent accreditation by laboratories.

⁹ Nulligravida describes women who have never been pregnant

¹⁰ Kollman *et al*, 2001 Blood. Accessed from:

<https://www.sciencedirect.com/science/article/pii/S0006497120587454>

- All proposed Australian HPC donor recruitment strategies and transition of buccal swab sample-based testing from overseas to Australian laboratories needs to be evidence-based.
- A 5-year plan to implement reform of adult HPC donor recruitment agreed by JHPCC in collaboration with stakeholders; ABMDR, Lifeblood, pathology providers and patient representative groups will deliver the increased target for HPC recruitment.
- The increase and expansion of HPC donor recruitment required to address the long-term strategic objectives of the National HPC Framework can be achieved through a combination of Lifeblood and ABMDR activities directed by the results of ethnicity and HLA diversity analysis of the national registry (described later):
 - Increasing HPC donor recruitment from new Lifeblood blood donor attendees, requiring high throughput molecular testing, will enable a higher proportion of new blood donors to also become HPC recruits (using blood-based HLA, blood group and CMV testing). This increased HPC recruitment will have a potential flow-on benefit for identifying additional platelet donors from those tested.
 - Utilising the planned implementation of low-resolution HLA and HPA testing of new blood donors (who are not currently HLA or HPA typed) to improve the pool of platelet donors for patients with rare HLA or HPA types. This testing could also identify additional potential HPC recruits, or platelet donors, from the existing blood donor pool based on their self-reported ethnicity.
 - HPC donor recruitment through fixed or mobile Lifeblood centres, or recruitment external to Lifeblood, using a combination of buccal swab (for HLA) and blood testing (for blood group and CMV). This option could necessitate additional test providers to upscale testing capacity.
 - ABMDR-led face-to-face community recruitment using only buccal swab samples and using overseas laboratories until domestic buccal swab-based testing is established.
- Increased laboratory testing capability through use of high throughput testing in Australia needs to be coupled with automation of processes to increase capacity to deliver test results in a timely manner. Digital transfer of test results is required as manual processing is a barrier to timely data provision to MatchPoint at the scale proposed.
- As HLA types are inherited, an individual's ethnicity provides an indirect indication of potential match between patient and donor, but HLA analysis of the registry is not currently performed. A new and ongoing analysis of HLA type data from the registry is required:
 - A baseline assessment of the relationship between registrant HLA type and self-reported ethnicity of existing ABMDR registrants should be performed to identify gaps in domestic donor coverage.
 - An unmet needs analysis of patient HLA data should be performed to identify HLA haplotypes not covered in the national registry, and for those recipients who were unable to be matched to a suitable domestic or international donor.
 - Thereafter, an annual donor audit and patient needs analysis should be performed to direct future recruitment targets and activities tailored to the most under-represented groups.
- The current classification of ethnicity used to describe ABMDR registrants should be assessed to ensure it is fit for purpose with sufficient granularity to direct HPC donor recruitment activities and consider changes that are consistent with reporting practices observed in other countries.

- A broader combination of recruitment strategies, settings, sample collection methods and testing are needed to achieve the increased recruitment aims. Systematic recruitment strategies to maximise participation in HPC donor recruitment, particularly for populations not currently adequately represented in the national registry, based on age, ethnicity and tissue-type status are required.
 - Diversification of recruitment activity would collectively aim to proportionately populate the national registry in line with the diversity of the Australian population.
 - Engagement of Aboriginal and Torres Strait Islander populations in HPC donor recruitment to fulfil their community needs requires coordinated activities performed using culturally safe practices. This should include engagement with formal bodies such as the National Aboriginal Community Controlled Health Organisations to facilitate testing in non-metropolitan communities, in addition to ongoing community-led recruitment activities.
- Consolidated and consistent messaging is needed across Lifeblood and the ABMDR to maximise reach with HPC donor recruitment activities that are tailored to the diverse Australian population mix, noting the complexity of geographic spread and accessibility. Recruitment messaging and advertising should be informed by the success of domestic activities and by best practice overseas.
- The messaging of the need for enhanced HPC donor recruitment activities needs to be concurrently contextualised with messaging on the contemporary success of donor matching and outcomes for HPC recipients.
- The HPC sector is inextricably linked to the supply of blood and blood-related products. Any changes to HPC donor recruitment should be integrated with changes in the management of blood donors, enabling the most efficient use of critically needed donors.
- The Advisory Group recognises the invaluable role the volunteer sector and community engagement activities play in educating the Australian community on the need for HPC donors. These organisations are integral to the ongoing success of HPC donor recruitment, and the provision of support for individuals awaiting HPC transplantation.

Proposed timelines for Implementation

Immediate actions

Substantially increase the target for HPC recruitment

Growth of the national registry is required to arrest the attrition of the preferred donor demographic to better meet the needs of Australian patients. Over a five-year period, to be consistent with comparable countries, the national registry should expand by 100,000 to 150,000 new recruits. This equates to an annual recruitment target of between 25,000 and 40,000 new HPC recruits. The expansion will aim to reduce the relative over-reliance of overseas sourced HPCs for Australian patients, and concomitantly may increase the utilisation of Australian HPC donors for recipients overseas.

This proposed increase in HPC donor recruitment does not aim to make the Australian HPC sector self-sufficient, as there will remain a continued need to use overseas donors for some patients that are not able to secure a matched donor within Australia.

Increase the recruitment of HPC donors via Lifeblood

There is an underutilised pool of new blood donor recruits registered with Lifeblood. During 2021-22 Lifeblood recruited approximately 56,000 new male and female blood donors aged 18-35 years. Existing blood donors aged 18-35 years can also be approached to become HPC donors, providing testing capacity is modernised and upscaled.

The Advisory Group recommends the JHPCC consider providing advice to the National Blood Authority to revise the annual target for Lifeblood blood donor recruitment upwards to increase the overall donor pool for blood and blood-related products to provide stability of the domestic supply, and which may also proportionally increase HPC recruitment.

Improve the data transfer from laboratories for the provision of data to MatchPoint managed by ABMDR

Manual processing of laboratory results for current ABMDR activities was identified in feedback from the Australian HLA laboratories as rate limiting to the rapidity of increasing domestic HPC donor recruitment testing.

The Advisory Group advises that optimisation of results management through automation of testing and results processing needs to be implemented in parallel with the expansion and modernisation of domestic laboratory testing options.

Implement buccal swab testing options at recruitment to increase the accessibility of Australians in joining the HPC registry

Buccal swab testing has been successfully used by overseas registries to recruit donors, and the STG pilot programs illustrated that this method of recruitment could be implemented in Australia alongside current recruitment by blood sample. Buccal swabs can be used to recruit Australians who are unable to, or may not consider attending a Lifeblood donation centre, thus providing greater accessibility to potential recruits who reside in regional and remote areas of Australia.

The Advisory Group recommends that buccal swab-based recruitment is implemented in Australia but is cognisant that current domestic laboratory capability and capacity is not yet optimal for onshore testing of buccal swabs. Overseas testing of buccal swabs by registry laboratories should be utilised until domestic capability is available, as testing of samples by Australian laboratories is overseen by Australian regulatory and accreditation frameworks.

Increase the domestic capability of Australian laboratories to test buccal swabs

There is a compelling public health need to improve the domestic laboratory testing capability and capacity of buccal swab-based blood group (ABO and Rh) and CMV status testing to facilitate increased HPC donor recruitment.

All three laboratories currently involved in HPC donor testing; Lifeblood, PathWest (Western Australia) and Pathology Queensland (Queensland) have indicated they would be capable of performing testing on buccal swabs. Validation and accreditation of laboratories to test buccal swabs via in-house *in vitro* diagnostic medical devices (IVDs) will require capital expenditure on laboratory equipment and personnel and may take around 6 months to complete.

The Advisory Group recommends that the current regulatory framework is applied to Class 4 IVDs to be used in buccal swab testing, and in the interest of public health requests the Therapeutic Goods Administration (TGA) utilise existing provisions available to reduce the associated assessment fees. While the domestic testing capacity is being increased for blood-based testing, and until full domestic buccal swab testing capability is established, the need for increased HPC donor recruitment can be partly met using overseas testing.

Widen the adult HPC donor age range eligibility at recruitment to 18-40 years

The Advisory Group recommends expanding the age range for HPC donor recruitment eligibility to 18-40 years of age to maximise the potential recruitment of the most HLA and ethnicity-diverse individuals required to meet the needs of the Australian recipient population.

Use evidence-based recruitment strategies to improve the ethnic and HLA diversity of donors on the national registry

A formal assessment of the current diversity of HLA and cultural background of HPC recruits in the national adult HPC registry should be performed by a clinical group with appropriate expertise, to act as a baseline for comparison, and to inform future recruitment activity. The ABMDR does not have capability to perform this activity and it is not currently undertaken.

The Advisory Group recommends that all future HPC recruitment and testing capability should aim to increase the numbers of HPC recruits and maximise both the HLA diversity (measured by haplotype or allele frequency) and ethnicity of the national registry, as assessed annually following the baseline analysis.

Due to the heterogeneous composition of the Australian population, the Advisory Group recommends that general HPC donor recruitment should also aim to increase the proportion of individuals who self-identify as being of mixed ancestry. This will likely increase the proportional yield of identifying HPC recruits with low frequency HLA haplotypes.

Short-term actions (within next 6 to 12 months)

Increase testing capacity of Australian laboratories

Lifeblood has indicated to the Commonwealth that through the introduction of high-throughput testing, existing testing capacity can be increased to between 25,000 and 50,000 individuals per year. This increase could encompass Lifeblood HPC donor recruitment (approximately 20,000 individuals per year) and external recruitment (e.g. in conjunction with the ABMDR or other stakeholders), using either buccal swab or blood for HLA testing and a concurrent, or later, blood test for blood group and CMV status (see Table 2 – Proposed 5-year plan to increase adult donor recruitment).

This testing strategy using a combination of buccal swab for HLA typing and blood test for ABO and Rh and CMV status would meet the standard for HPC donor recruitment testing set by ABMDR and

be performed in Australia. Implementation would require capital expenditure on laboratory equipment and laboratory accreditation for HLA testing (approximately 6 months from installation), plus systems for automation of results transfer.

The Advisory Group is aware that testing of donors currently recruited by Lifeblood in Queensland and Western Australia is performed by state pathology laboratories (Pathology Queensland and PathWest). Increased testing capacity of testing by these laboratories would also be required.

Lifeblood's planned implementation of the Universal Blood Donor Testing (UBDT) array will enable low-resolution 2-field HLA testing from among a large pool of blood donors not currently HLA typed, to identify additional potential HPC recruits and platelet donors with rare HLA and HPA haplotypes who are not currently identifiable. Where a specific patient with a rare HLA configuration requires a HPC transplant or matched platelets, the pool of individuals who are blood donors but not HPC recruits can then be searched for potential HLA matches (at 2-field resolution) and if consented could proceed to complete HLA/HPA testing. Those existing blood donors not yet HLA typed could be consented to join the national registry if identified as a potential match based on self-reported ethnicity; they would then undergo initial 2-field HLA testing and completion of HLA typing (to the ABMDR standard) if found to be an appropriate match.

If blood donors are identified through the UBDT as having "rare" haplotypes missing from the national registry, their consent and full testing should be performed up front, so they can be fully uploaded into the national registry and be available for a comprehensive search for a selected patient seeking a suitable donor.

Messaging and advertising for HPC donor recruitment needs to be consolidated and enhanced

Consistent messaging is required by entities performing HPC donor recruitment activities. This should involve messaging that is tailored to the diverse Australian population, noting the complexity of geographic spread and accessibility. Recruitment messaging and advertising should be informed by the success of domestic activities (including that for blood donor recruitment) and by best practice overseas and be properly funded to achieve the proposed increase in recruitment.

The Advisory Group noted that there is a discrepancy in the messaging that is directed to HPC donor recruitment versus that for recipients. HPC donor recruitment messaging on the need for increased donors may be interpreted to mean there is a lower likelihood of a HPC donor being found and cannot encompass the complexity of contemporary donor selection. The separate needs for donor recruitment and transplant recipient messaging needs to be clearly recognisable, with accurate information for recipients and their families on the likelihood of HPC donor matching, noting that permissive mismatching of HPC donors enables a potential use of existing HPC registrants.

Given the lower age limit for HPC donor recruitment, consideration should be given to improving messaging of becoming a HPC registrant and/or blood donor across a diverse range of high school and community settings, using a mixture of face-to-face and online messaging, informed by the success of programs in other countries.

Alignment of HPC sector recruitment and testing (adult and cord blood) into a National Strategy for HPC recruitment

The Advisory Group notes there is a review of the Australian cord blood sector currently in progress but is not in the remit of this advice. It is advised that any proposed changes to the cord blood sector is considered in conjunction with the implementation of recommendations for adult HPC donor recruitment in the Australian HPC sector.

Long-term actions (12 months onwards)

Use evidence-based recruitment strategies to improve the ethnic and HLA diversity of the national registry

Ongoing annual/biannual re-analysis of the HLA and ethnicity diversity, registrant age distribution should be performed to assess the comparative success of directed recruitment strategies. This analysis would then inform recruitment targets, messaging, advertising, and testing required for the subsequent year.

Undertake a regular needs analysis and audit of HPC recruitment strategies to inform future recruitment strategies and targets

Given the changing therapeutic landscape of treatment options for patients with haematological malignancies, and emerging gene therapies for hereditary conditions, a needs analysis needs to be performed in conjunction with the HLA/ethnicity diversity analysis described above to inform future recruitment targets and recruitment options. The needs analysis should also identify gaps in registry coverage for recipients who are unable to be matched to a suitable domestic or international HPC donor.

Improve the retention of HPC donors and reduce barriers to donation

Ongoing active contact with HPC registrants by ABMDR is required to ensure their willingness to remain a HPC donor on the national registry. This will also ensure personal contact details remain valid, given the average time between initial registration and donation may be several years.

The Advisory Group recognises that there may be barriers to donation as a proportion of the optimal donor pool could be in transient employment, accommodation, or geographically disparate from services. This may impair their ability to attend a facility for provision of samples for verification testing and/or undertake HPC donation when called upon due to loss of income, travel expense or other unidentified barriers.

The Advisory Group suggests that the current process/payment for travel expenses for HPC donation be reviewed to also consider whether loss of income could be reimbursed.

Table 2. Summary of current and indicative HPC donor recruitment targets and options for future testing

The indicative options for increasing HPC donor recruitment testing, and projected target recruitment are summarised in the table below.

	Mode of Recruitment			Recruitment target (achieved)	Recruitment target projection over time					Estimated total recruitment over five years
					Year 1 (2023-24)	Year 2 (2024-25)	Year 3 (2025-26)	Year 4 (2026-27)	Year 5 (2027-28)	
2020-21	Strength to Give pilot buccal recruitment			6,000/yr (5,826)	N/A	N/A	N/A	N/A	N/A	N/A
Current Recruitment	All recruited via blood sample by Lifeblood (majority are blood donors)			5229/yr (7,845)	7,845	7,845	7,845	7,845	7,845	39,225
Future HPC recruitment options, indicative service volumes	Blood donor & HPC recruit (by Lifeblood)	Lifeblood	Blood: HLA, ABO CMV	30,000/yr	15,000	25,000 to 50,000*	25,000 to 50,000*	25,000 to 50,000*	25,000 to 50,000*	115,000 to 215,000*
	HPC recruit only (by Lifeblood)	Lifeblood	Blood: HLA, ABO, CMV							
	Community – metropolitan area	Lifeblood / Path West/ Other pathology providers	Buccal: HLA Blood: ABO, CMV 2-step model							
	Online/Community – regional and remote communities	Overseas testing	Buccal: HLA, ABO and CMV	~10,000/yr	10,000					10,000
	Online/Community – regional and remote communities	Australian laboratory	Buccal: HLA, ABO and CMV	10,000/yr		10,000	10,000	10,000	10,000	40,000

*Based on Lifeblood implementing additional laboratory capacity and accrediting laboratory workflow for NGS testing

**Based on buccal swab HLA testing by laboratory capacity per year of: SA 800 tests, VIC 5000 tests, NSW 5000 tests, WA 5000 tests & QLD 2000 tests. This laboratory capacity is dependent on additional de-capping robots in VIC and NSW, plus workforce for laboratory processing in all jurisdictions.

Shading reflects the implementation complexity associated with potential regulatory changes and accreditation processes. Green – NIL regulatory changes required as testing is within current accreditation, blue –no regulatory oversight as testing performed oversea, orange – regulatory changes required, and accreditation processes may be protracted.

Background

As outlined in the National Strategic Action Plan for Blood Cancer¹¹, the therapeutic landscape for haematological malignancies has rapidly expanded beyond solely chemotherapy over the last two decades to include chemo-immunotherapy regimens, chimeric antigen receptor-T-cells (CAR-T cells), and bi-specific antibody products. Despite the increase in registered and experimental therapeutic options for patients with haematological malignancy, HPC transplantation remains an essential (and sometimes only) therapeutic option for many patients, depending on disease-type, degree of response to prior line(s) of therapy and remaining therapeutic options. HPCs also provide a necessary option in the management of a range serious and/or life-threatening heritable conditions of bone marrow failure or immunodeficiency.

The number of HPC transplants performed for Australian paediatric and adult patients over a five-year period is shown in Table 3.

Table 3. Proportional split of adult and paediatric HPC transplants over a 5-year reporting period.¹²

Recipient	Year of HPC transplant					Total
	2017	2018	2019	2020	2021	
Adult	302	323	344	350	485	1,774
Paediatric	74	78	68	68	88	376

Among all HPC transplants in Australia, an unrelated HPC donor is used in 70% of adult recipients and 80% of paediatric recipients. Where a related HPC donor is identified as an option for a patient, directed testing of their immediate family members is undertaken i.e. separate from general HPC donor recruitment. For adult transplant recipients using a related HPC donor, most donations are from a child or sibling (77% total) whereas for paediatric recipients the parent comprises the largest HPC donor source (80%)¹³.

The clinically optimal demographic for unrelated HPC donors is males aged 18-35 years, as this age-group have been demonstrated to achieve improved transplant outcomes compared with those from older HPC donors¹⁴. The preference for males is related to their lower likelihood of being sensitised to allogeneic antigens compared to females who may have been pregnant.

¹¹ National Strategic Action Plan for Blood Cancer, Leukaemia Foundation 2020, accessed from: <https://www.leukaemia.org.au/national-action-plan/ndation>

¹² Data source: Australian and New Zealand Transplant and Cellular Therapies Register (ANZTCTR) Annual reports

¹³ Data source: Australian and New Zealand Transplant and Cellular Therapies Register (ANZTCTR)

¹⁴ Kollman *et al*, 2001 Blood, accessed from: <https://www.sciencedirect.com/science/article/pii/S0006497120587454>

Current national HPC registry size

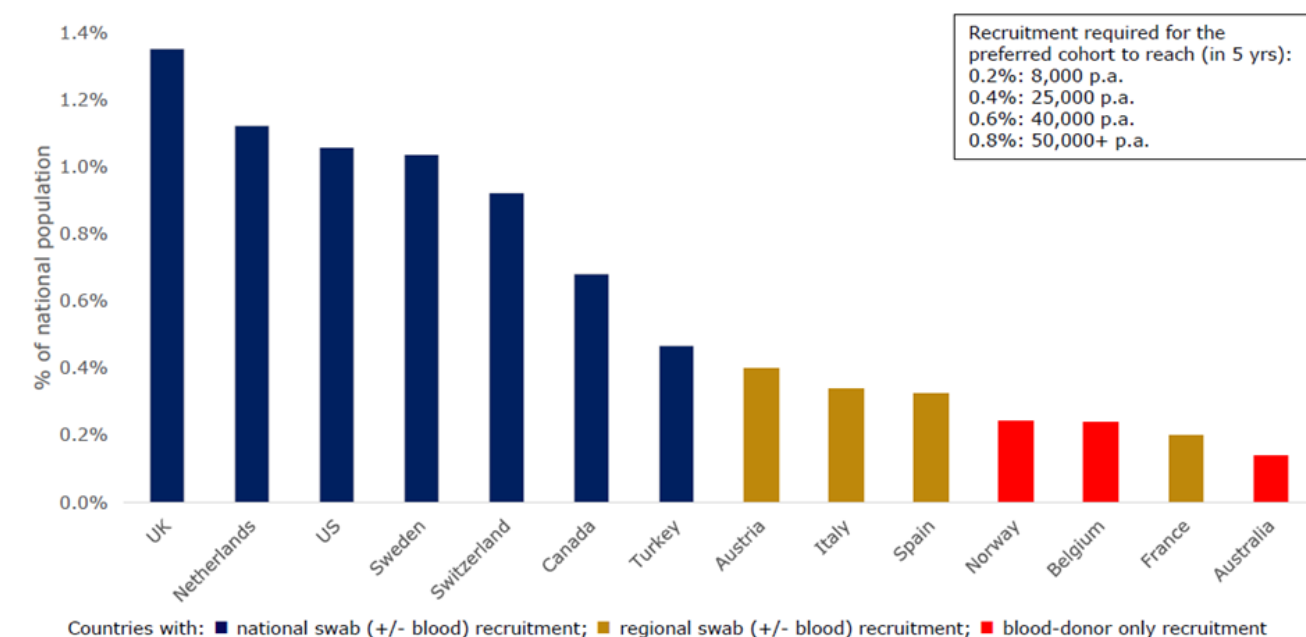
In 2021, over 70% of unrelated HPC transplants in Australia used internationally sourced HPCs and only 11% of HPC donors on the national registry were the clinically desirable demographic of 18-35 year-old males (preferred demographic)¹⁵.

During 2022, the ABMDR commenced an “outreach program” to identify donors on the national registry that were uncontactable or who wished to be removed from the national registry as part of national registry maintenance.

The ABMDR most recently reported the adult HPC donor registry size, as of 31 December 2022, as comprising 176,537 donors. However, following removal of donors who were uncontactable or wished to be removed, the effective total donor registry size will be 131,806 donors, with 52,834 (40.1%) donors being the preferred demographic. The current gender split of the 18-35 year old donors is 40% male 60% female.

Data from the WMDA (Figure 1, provided by ABMDR) illustrates countries with comparable health systems to Australia whose registries comprise of preferred donors at between 0.4-0.6% of the national population, equivalent to an Australian pool of 125,000 to 200,000 individuals. Each country determines the age-range of HPC recruits and donor recruitment strategies considered appropriate for its own population mix and likelihood of identifying a matched HPC donor.

Figure 1. Preferred donor cohort as a proportion of the national population by country and recruitment method (average 2016 to 2020).¹⁶



Current Australian HPC recruitment strategy

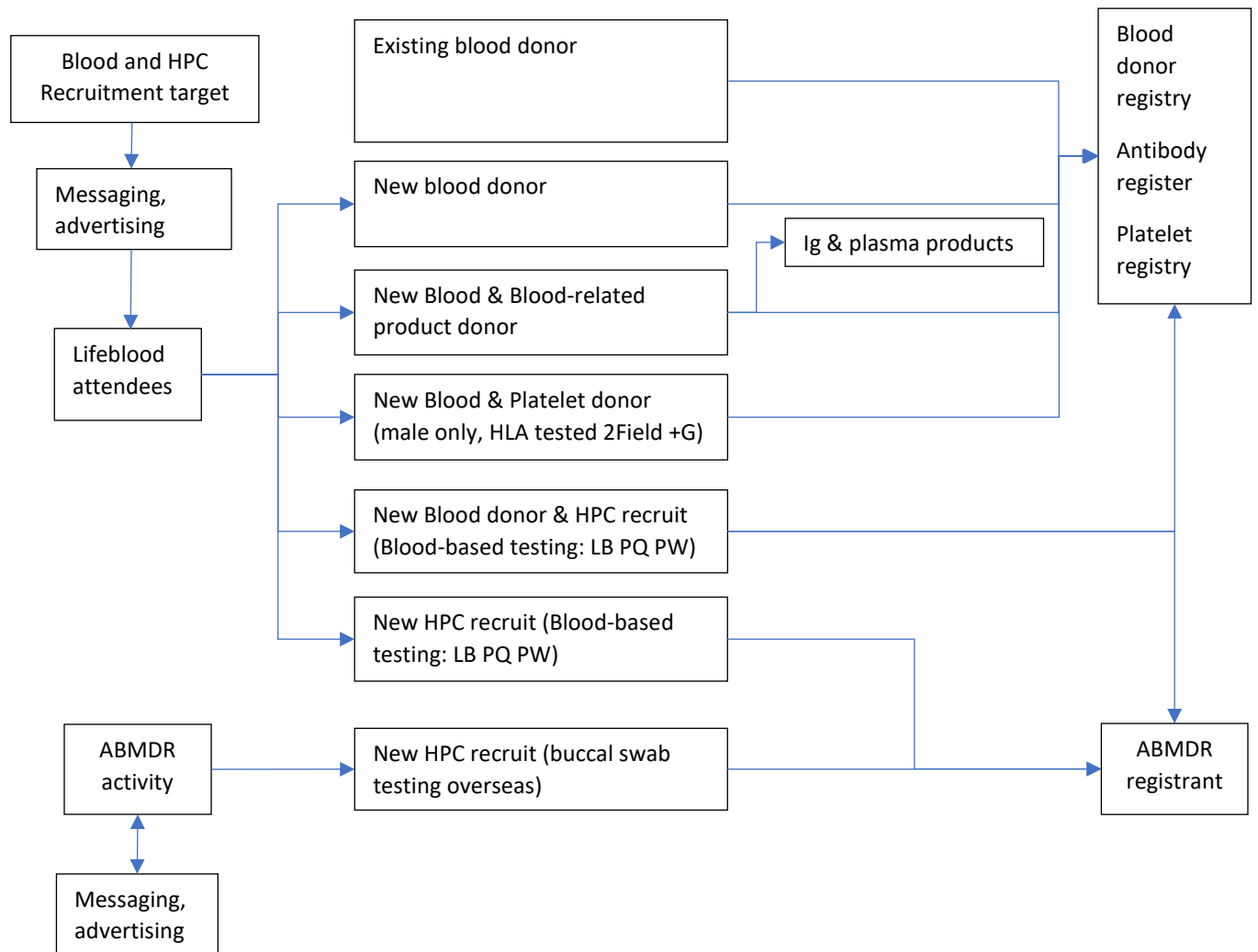
The Australian haematology and HPC recruitment sectors are inextricably linked to the domestic supply, and demand for, blood and blood-related products. All non-HPC treatment options in the management of blood cancers risk suppression across one or more cell lines, requiring management

¹⁵ ABMDR Annual Registry Performance Report 2021

¹⁶ Data from the WMDA Global trends report, 2021 provided by ABMDR October 2022

with blood-group matched red cells, tissue-typed platelets, immunoglobulin, or other blood-related products. Lifeblood has recruited approximately 90% of all HPC registrants, with the remainder through ABMDR-led buccal swab activities. The current recruitment strategies through Lifeblood and ABMDR, showing the relationship with other Lifeblood donor activity is shown in Figure 2.

Figure 2. Schematic of current HPC and blood donor recruitment



In Australia, blood donors who present to a Lifeblood donation centre may also elect to become a donor of platelets, plasma, immunoglobulin and/or HPCs. The Lifeblood HPC donor recruitment target is currently set by the ABMDR, with the ABMDR undertaking HPC donor recruitment activities using buccal swabs separately. Lifeblood does not currently report the proportion of their HPC recruits that attend solely to be HPC donors (noting there are different eligibility criteria in becoming an HPC donor over a blood donor).

The current level of recruitment of blood donors provides for the ongoing domestic supply of blood and blood-related products. However, the provision of domestic blood and blood-related products is less stable than pre-COVID and the contribution of Australian-fractionated immunoglobulin to rising national demand, in part due to B-cell depleting therapies for haematological malignancies, has

reduced for the first time in five years¹⁷. Maintenance of the current supply of blood and blood-related products from Australian blood donors is essential when considering change to HPC donor recruitment.

Lifeblood performs approximately 63% of the HLA typing on HPC recruit samples per year through a semi-automated workflow on whole blood samples. The state pathology HLA typing laboratories in Queensland and Western Australia processes the remaining donors.

The current target for HPC recruitment through Lifeblood is 5,300 per year, with 7,845 HPC donors recruited in 2020-21. Even though Lifeblood has recruited more HPC donors than the target provided by ABMDR, continued attrition of the preferred HPC donor pool would occur and over the next five years would comprise approximately 39,225 donors.

The ABMDR advised a minimum of 8,000 new HPC recruits are required per year to arrest the current attrition rate of optimal donors, occurring due to ageing of the donors in the national registry and low recruitment. However, this level of recruitment would not increase the national registry size¹⁸.

The ABMDR has undertaken two pilot programs using buccal swabs at HPC donor recruitment, to test whether buccal swabs could be implemented in Australia to improve HPC donor recruitment. STG1 was funded directly by the ABMDR and recruited 5,540 individuals between July 2019 – May 2020. Testing of swabs was performed in the USA by Histogenetics (with a swab not listed on the Australian Register of Therapeutic Goods (ARTG)).

By April 2020, STG1 had yielded 4,481 new HPC recruits (36% male) with face-to-face recruitment being influential in recruiting males of the preferred age range (Table 4).

Table 4. The recruitment of male and female donors during STG1 by recruitment method.

Recruitment Method	Recruits: Number	Male: Number (%)	Female: Number (%)
Face to face	980	725 (74)	255 (26)
Online	3,501	896 (26)	2,605 (74)
Total	4,481	1,621 (36% average)	2,860 (64% average)

STG2 was funded by all governments (\$625,000) and recruited 5,527 individuals between July 2020-April 2021. The buccal swabs used had to be listed on the ARTG. PathWest performed the HLA typing, whilst Histogenetics performed the ABO and Rh blood group and CMV status testing.

Australia is a country of mixed ethnicity, comprising of indigenous people, descendants of European settlement and immigrants from other nations making Australia their home. In 2021, Aboriginal and Torres Strait Islander First Nation people accounted for 3.2% of the population¹⁹, with variation

¹⁷ National Blood Authority Annual Report 2021-2022, accessed from: <https://www.blood.gov.au/sites/default/files/NBA0861%20%20NBA%20Annual%20Report%20202122%20-%20WCAG.pdf>

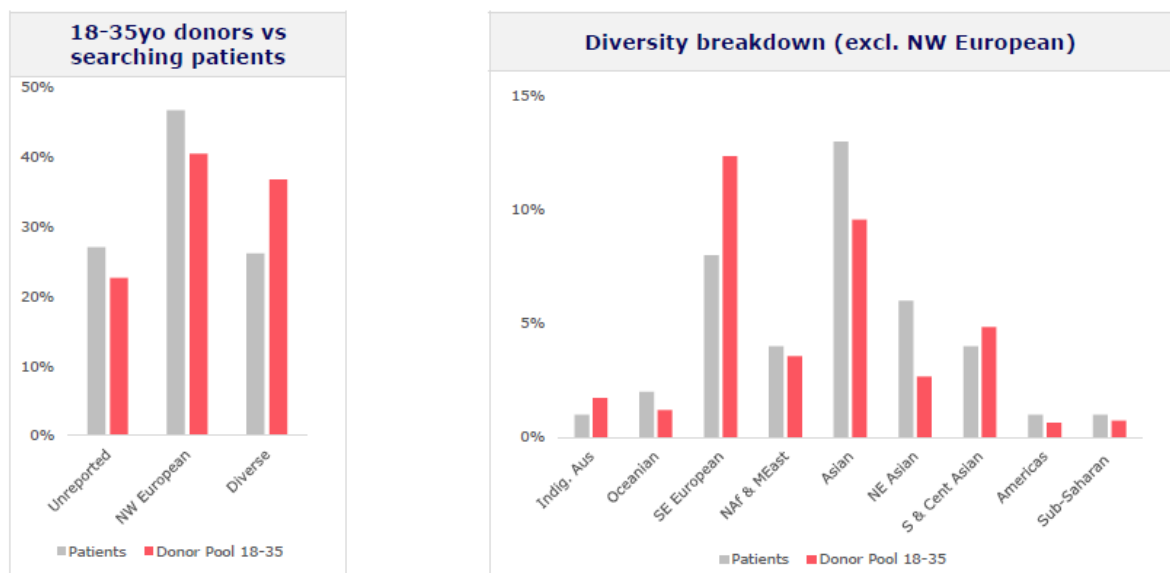
¹⁸ ABMDR presentation to the Advisory Group - 14 October 2022

¹⁹ Australian Bureau of Statistics data – Aboriginal and Torres Strait Islander population summary 2021, accessed from: <https://www.abs.gov.au/statistics/people/aboriginal-and-torres-strait-islander-peoples/estimates-aboriginal-and-torres-strait-islander-australians/latest->

across States and Territories. In 2021, 29.1% of Australia's resident population were born overseas (7.5 million migrants)²⁰. Australian patients from non-Caucasian and Indigenous populations are less likely to find a suitably matched Australian donor in the current register²¹ (Figure 3).

Since 2021, Lifeblood has been requested by ABMDR to target the preferred HPC donor demographic (male: 18-35 years). Lifeblood collects primary and secondary self-declared ethnicity from blood donors. In FY2021-22, 93,431 new blood donors were recruited by Lifeblood across Australia. In the new blood donor pool, 24,904 (26.55%) were male and aged 18-35 years of age. 42% of the new male donors aged 18-35 years identified British/Irish ethnicity as their primary ethnicity listed, with 40% of these donors listing non-British/Irish ethnicity as their secondary ethnicity²². This indicates the Australian blood donor pool has donors with mixed ethnicity who could be recruited to the national registry.

Figure 3. Ethnic diversity of patients requiring transplant and the HPC donor pool



Source: ABMDR. 'Diverse' donors include those not exclusively NW European.

There was insufficient evidence from the STG pilot programs that donors recruited differed in self-reported ancestry to those recruited by Lifeblood, thereby improving the diversity of the registry. However, 39% of donors recruited through the STG pilot programs self-declared ethnicity was not North-West European, reflecting populations that are currently under-represented in the ABMDR (Table 5). From the STG ethnicity data, those recruits that did not have an ethnicity specified are assumed to be from the commonest populations.

[release#:~:text=The%20final%20estimated%20resident%20Aboriginal%20and%20Torres%20Strait,the%20estimate%20of%20669%2C900%20for%2030%20June%202011.](#)

²⁰ Australian Bureau of Statistics – Australia's Population by Country of Birth, 2021 accessed from:

<https://www.abs.gov.au/statistics/people/population/australias-population-country-birth/latest-release>

²¹ Data provided by ABMDR - October 2022.

²² Data provided by Lifeblood – November 2022

Table 5. Ethnicity data from ABMDR STG recruitment programs

Descriptor	Data: Number (%)
Total searchable donors (both STG)	11,067
Number of male recruits (% total)	3,671 (33%)
Recruits with North-West European ethnicity (% total)	(34%)
Recruits with unspecified self-reported ethnicity (% total)	(27%)
Proportion of recruits categorised a category 'diverse', cumulatively reflecting low incidence ethnicity groups	4,315 (39%)

The ABMDR has advised it does not have the capability to analyse the national registry to determine if the HLA diversity of the national registry mirrors the ethnic diversity of the registry and identify where any gaps exist.

Standards for testing at HPC recruitment – current practice

The WMDA sets minimum standards for testing at recruitment and coordinates the results of HPC recruits worldwide, and states that “all testing must be carried out in a manner to ensure the accuracy of the data”. The testing performed in selected other jurisdictions compared to Australia is shown in Appendix 1. The ABMDR standard mandates a higher resolution of HLA typing than the WMDA standard, and preferences blood group and CMV testing at initial recruitment rather than later at donor selection when verification typing is undertaken (Table 6). Of note, for the ABMDR requirements, the timing of HLA testing as compared to blood group and CMV testing is not specified and may plausibly be undertaken separately.

Table 6. Testing Standards at HPC donor recruitment

Testing at HPC donor recruitment	WMDA standard	ABMDR standard
HLA testing	A minimum of HLA-A, -B, -C, -DRB1 DNA-based typing results must be defined prior to listing newly recruited donors.	HLA-A, -B, -C, DRB1, -DQB1 and DPB1. 2 field NGS plus G-code as a minimum.
Blood group	ABO and Rh blood group of donors must be done at the verification typing stage if the donor's blood group has not been previously determined	Molecular ABO and RhD genotyping or serological blood group test
Cytomegalovirus	Not required at initial recruitment. But performed at verification testing.	IgG detection

Following publication of the National HPC Framework in November 2021, all Australian laboratories now perform high resolution HLA typing by NGS which exceeds the standard defined by the ABMDR for initial HPC donor recruitment. NGS by long-range polymerase chain reaction (PCR) using high throughput testing has been reported to deliver HLA results from buccal swab-based testing that are unambiguous, as is required for HPC transplantation, despite a lower DNA sample content compared with blood-based testing²³.

²³ Yin *et al*, 2016. PLoS One. Accessed from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5087893/>

The reference standard of blood-based test for CMV IgG identifies evidence of past infection with CMV. The requirement for CMV IgG detection at initial recruitment was introduced in 2021 and testing is consistent with testing performed at recruitment by comparable overseas registries.

It should be noted for the purposes of recruitment, that the sensitivity of CMV IgG testing performed on buccal swabs is lower than from blood samples, and that testing on buccal swabs is seen as a guide for the initial selection of a potential HPC donor for a specific recipient rather than a diagnostic test. Similarly, when comparing blood-based CMV testing with buccal swab-based CMV testing, there is a small proportion of discordant test results²⁴. This variation in sensitivity and concordance is considered acceptable given that all CMV testing is repeated at verification testing and this can be performed rapidly where the transplant is considered time sensitive.

Australian regulation and accreditation of HPC donor recruitment testing

The TGA regulates pathology tests and donor screening tests as *in vitro* medical devices (IVD), which are a subset of medical devices. IVDs are classified according to the intended purpose of the device and with regards to personal or public health risk. The IVD framework has a four-tier classification structure with Class 1 IVDs representing lower risk products and Class 4 IVD medical devices being the highest risk products.

All commercially supplied laboratory tests for HLA, CMV and blood group testing performed to recruit donors to the national registry or prior to HPC transplantation are required to be included in the ARTG, before they can be legally supplied in Australia. Application/audit fees and annual charges apply.

Laboratory developed or modified commercial tests are regulated as in-house IVDs. Laboratories must evaluate their Class 1-3 in-house IVDs under their National Association of Testing Authorities (NATA)/The Royal College of Pathologists of Australasia (RCPA) accreditation in accordance with *ISO15189 Medical Laboratories – Requirements for Quality and Competence* and *Requirements for Development and Use of In-house IVDs*²⁵ published by National Pathology Accreditation Advisory Council (NPAAC) and notify their Class 1-3 in-house IVDs to the TGA.

All HLA typing tests are regulated as Class 3 IVDs and may be utilised by laboratories accredited to perform this testing. Currently, all commercially supplied laboratory tests for HLA typing are intended for use with blood samples. There are no commercial devices approved for HLA typing using buccal swabs. PathWest, Pathology Queensland and Lifeblood are accredited to extract DNA from buccal swab samples for HLA typing using Class 3 in-house IVDs.

Consistent with international regulatory alignment, all donor screening tests for transmissible infectious diseases and ABO and RhD blood group testing are regulated as Class 4 IVDs. Class 4 commercial IVDs and Class 4 in-house IVDs that are developed or modified from commercially supplied IVDs require inclusion in the ARTG. There are no commercially supplied Class 4 IVDs, or Class 4 in-house IVDs for ABO and RhD genotyping, or CMV IgG testing that are approved in Australia for testing buccal swab samples (Table 7).

All Australian tissue typing laboratories use NGS or massive parallel sequencing which can deliver the high-resolution HLA typing on blood samples, exceeding the level of resolution defined in the

²⁴ Behrens *et al*, 2021. Journal of Infectious Disease. Accessed from: <https://professional.dkms.org/research-publications/publications/behrens2020>

²⁵ <https://www1.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-dhaivd-2018>

ABMDR standard above. All current HLA testing for ABMDR purposes is reported to 3 fields, which is above the ABMDR standard of 2 field plus G code.

Table 7. Current capability and capacity of recruitment sample testing (Domestic versus Overseas).

Test	ABMDR standard	Australian laboratory capability by sample type		US or German laboratory capability
		Blood	Buccal-swab	Buccal-swab
HLA testing	HLA-A, -B, -C, DRB1, -DQB1 and DPB1. 2 field NGS plus G-code as a minimum.	Capacity for current testing	Limited capacity for current testing (PathWest & Lifeblood)	Capacity
ABO and RhD Blood group	serological blood test	Capacity for current testing	N/A	N/A
	Molecular ABO and Rhesus D genotyping	Capacity for current testing	No current domestic capability	Capacity
Cytomegalovirus	IgG detection	Capacity for current testing	No current domestic capability	Capacity

Laboratories that manufacture Class 4 in-house IVDs must lodge an application for inclusion in the ARTG with the TGA, and can use different conformity assessment pathways to support their application:

1. NATA accreditation, which meets the requirements of ISO15189 and NPAAC standard for the Development and Use of In-house IVDs
2. Code of Good Manufacturing Practice (GMP) for Blood and Blood Components, Human Tissues and Human Cellular Therapy Products (GMP manufacturing licence held by laboratories providing donor screening services for the tissue bank sector)
3. TGA conformity assessment, which meets the requirements of *ISO13485 Medical Devices – Quality management systems – Requirements for regulatory purposes*

The laboratory must have available technical documentation which supports the analytical and clinical performance of their Class 4 in-house IVDs and pay an application fee of \$1,098 for ARTG.

Assessment fees²⁶ for each individual test also apply, however there are provisions which allow for 70% reduction in assessment fees when requested, if it is in the interest of public health and it would not otherwise be commercially viable if the full fee were paid:

- Assessment fee for Class 4 in-house IVDs for CMV testing - \$22,387 (can be reduced to \$6,720)
- Assessment fee for Class 4 in-house IVDs for ABO or RhD genotyping - \$16,621 (can be reduced to \$4,990)
- Assessment fee for Class 4 in-house IVDs undergoing TGA conformity assessment (i.e. pathway 3 described above). Fees are consistent with applications for conformity assessment for commercial manufacturers and is therefore the least-preferred pathway for laboratories with Class 4 in-house IVDs.
- There are no annual charges or on-going fees associated with Class 4 in-house IVDs included in the ARTG.

²⁶ TGA application and assessment fees stated are applicable to 2023-24 financial year.

Potential Future National HPC Donor Recruitment Strategy

Presently, HPC donor recruitment is predominately through two separate systems with insufficient coordination: individuals present to a fixed or mobile Lifeblood collection centre as a potential blood donor, or through ABMDR-directed donor recruitment drives undertaken in conjunction with or without patient representative groups. Lifeblood has a recruitment team to enable new or existing blood donors to also become donors of platelets, immunoglobulin, plasma and/or HPCs.

A formalised national strategy for ongoing, recruitment and service planning for HPC donor recruitment should be established and enacted, by a single entity to direct HPC donor recruitment (in line with the National HPC Framework). This strategy should be informed by the composition of existing ABMDR registrants and also based on the need to populate the national registry to primarily fulfil domestic transplant needs given the diverse population structure of Australia. Planning should consider the recruitment settings and capacity to deliver efficient services through the combination of walk-in attendance at fixed or mobile centres, community recruitment in regional and remote settings, and a need to respond to requests for reactive HPC donor recruitment driven by patient support groups.

A proposed schematic of proposed options for future HPC donor recruitment that fully integrates analysis of the registry with all recruitment method is provided in Figure 4.

Standards for testing of samples at HPC donor recruitment – future practice

The Advisory Group considered that HLA typing at recruitment is the most clinically significant test that a clinician will use to select the most appropriate donor from an initial donor search report for verification testing (VT). The resolution of HLA typing currently performed is appropriate if it is visible to the transplant physician in the registry search reports.

The donor's ABO and Rh blood group and CMV status is clinically useful information to have upfront.

CMV testing at initial recruitment has the lowest utility of the three recruitment tests (Table 6) but should remain at recruitment for consistency with comparable international registries. All potential HPC donors have their CMV status retested at the time of VT prior to HPC donation, and that CMV status at this later time-point is influential on the survival outcome of an HPC transplant recipient²⁷.

The domestic laboratory capability to perform all three recruitment tests on buccal swabs needs to be developed. This needs to occur within the current regulatory frameworks to ensure oversight of testing is maintained.

Laboratory accreditation required to enable a transition from partial to full buccal swab testing in Australia

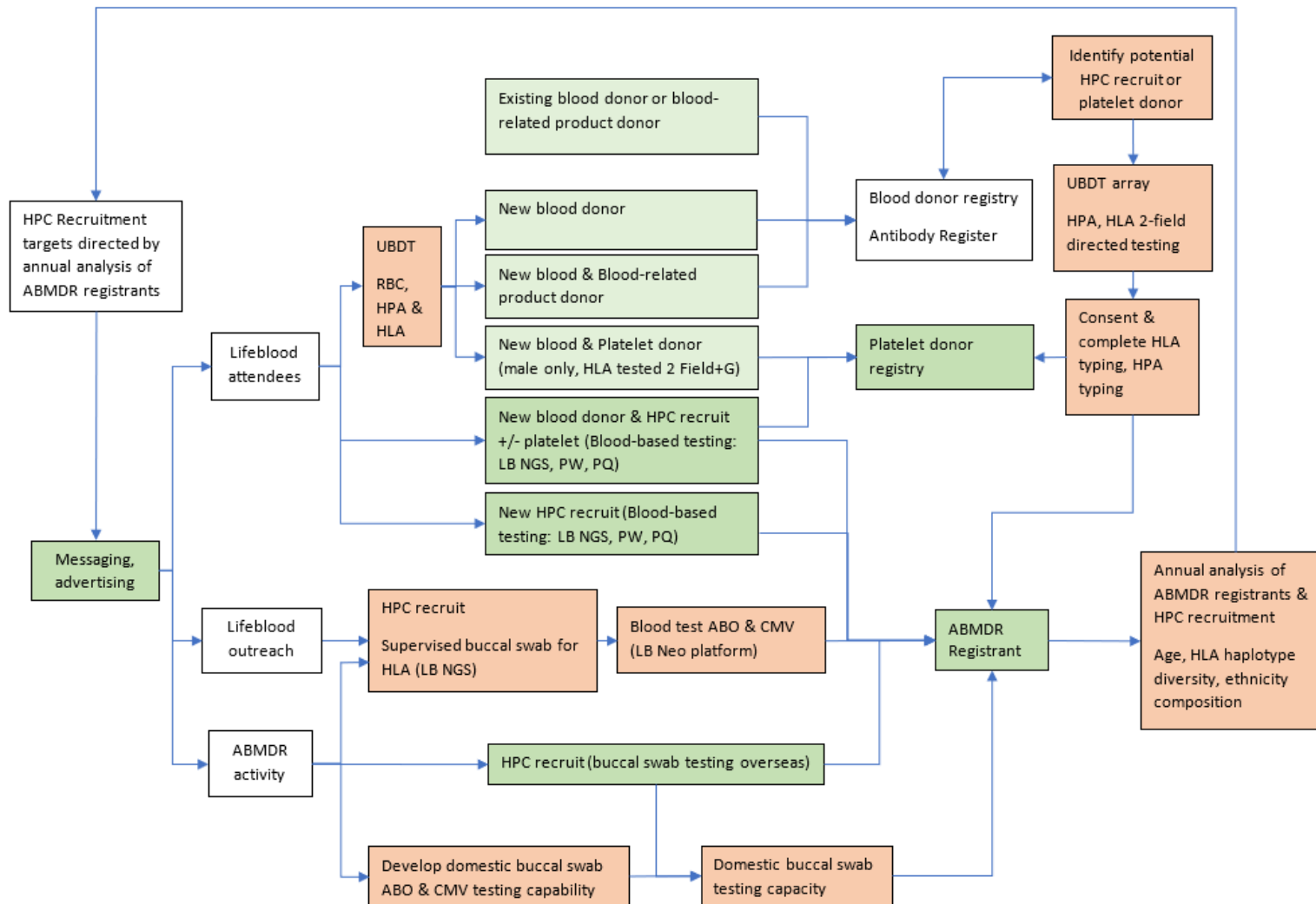
HLA typing on buccal swabs

Buccal swab-based DNA testing for HLA status (at any resolution) only requires laboratory accreditation for a given test platform, through NATA, and aside from the requirement to validate buccal swabs as an additional sample type, is not considered a barrier to implementation of buccal swab testing.

Lifeblood and Pathology Queensland have indicated that they would be willing to develop additional laboratory capacity to increase HLA testing using a buccal swab-based sample.

²⁷ Ljungman *et al*, 2014. Clinical Infectious Disease. Accessed from: <https://pubmed.ncbi.nlm.nih.gov/24850801/>

Figure 4. Schematic of proposed HPC recruitment that integrates national registry analysis with recruitment method.



Legend: Green = enhanced current activity, orange = new activity. LB = Lifeblood, PQ = Pathology Queensland, PW = PathWest, NGS = next generation sequencing, RBC = red blood cell antigen, HPA = human platelet antigen, HLA = human leucocyte antigen, UBDT = universal blood donor testing

Blood group & Rhesus DNA testing on buccal swab

The TGA assessment fee is identified as a barrier to device manufacturers in bringing novel test devices for use in Australia for the intended purpose of testing HPC recruits. The Advisory Group advises the JHPCC and TGA that there is a sufficient and compelling public health need for improved access to HPC testing capacity in Australia to warrant that the assessment fees for buccal swab-based ABO and RhD blood group testing is reduced to the extent possible. Advice was received from the TGA that available provisions for fee reduction could be applied to any Class 4 in-house IVD applications received from laboratories immediately following a recommendation from the Advisory Group.

CMV testing on buccal swab

The Advisory Group identified the TGA assessment fees as a barrier to device manufacturers in bringing novel test devices for use in Australia for the intended purpose of testing HPC recruits. The Advisory Group advises the JHPCC and TGA that there is a sufficient and compelling public health need for improved access to HPC testing capacity in Australia to warrant that the assessment fees for buccal swab based CMV immunoglobulin testing is reduced to the extent possible. Advice was received from the TGA that the available provisions for fee reduction could be applied to any Class 4 in-house IVD applications received from laboratories immediately following a recommendation from the Advisory Group.

The type and capacity of current testing required by ABMDR at initial HPC donor recruitment is summarised in Table 7.

TGA and NPAAC advice confirmed there is a need for laboratories to identify and validate every buccal swab type proposed for use in HPC donor recruitment. The issue of sample stability during transport would need to be considered in assessing test performance. Australian laboratories would need to establish a minimum yield for test sensitivity and specificity in comparison to blood testing to minimise risk of test result misclassification. Lifeblood have stated that they would need to determine the swab type for HLA testing for any expansion of testing to ensure quality of testing, rather than be directed by the ABMDR on the swab type used for HPC donor recruitment.

The NPAAC standard *“Requirements for medical testing for human genetic variation”* published by the Australian Commission on Standards and Quality in Healthcare (ACSQHC) ²⁸ includes the statement that “Specimens collected by the patient are not ideal for nucleic acid tests due to an increased risk of pre-analytical errors and specimen contamination”. Unsupervised (i.e. self-collected) buccal swab samples for HLA and molecular genotyping of blood groups would fall under the remit of this statement, and is therefore not considered the optimal process for buccal swab sample collection. Although the COVID-19 pandemic has required a large percentage of the population to develop competence in self collection for at-home tests, here is still a potential risk for misidentification of HLA status via inadvertent exchange or mislabelling of samples. Samples could also be taken incorrectly (i.e. a saliva sample obtained instead of a buccal cell sample). Therefore, validation of self-collection kit instructions and sample transport stability is required to be completed by the laboratory and these aspects should be reviewed as part of the in-house Class 3 IVD accreditation process by either NATA or TGA review of in-house Class 4 IVDs.

²⁸ NPAAC accreditation standard (Third Edition, 2022), accessed from: <https://www.safetyandquality.gov.au/publications-and-resources/resource-library/requirements-medical-testing-human-genetic-variation-third-edition>

All laboratories have stated that they would need to determine the swab type for HLA testing for any expansion of testing to ensure quality of testing, rather than be directed by ABMDR on the swab type used for HPC donor recruitment.

Future testing capacity in Australia to meet the increased HPC donor recruitment target

The estimated increase in recruitment (100,000 to 150,000 new recruits over 5 years) needed for Australia to have preferred donors at the same proportion as other comparable countries requires Australian laboratories to substantially increase their capacity to perform the number of tests required.

Advice received from the Australian laboratories involved in HPC donor recruitment testing is that current laboratory testing capacity is not limited by DNA sequencing capacity, but that the implementation of buccal swab processing would be rate-limited by:

- 1) Dry or wet buccal swabs and DNA extraction failure rates
- 2) Need for additional de-capping and processing DNA extraction robots
- 3) Additional full time equivalent (FTE) to book in and process additional samples even if semi-automated
- 4) Additional FTE and workflows for reporting increases in test turnover
- 5) The manual booking system for new ABMDR donors which is inefficient and would need modification for high throughput testing systems.

However, with the additional personnel, provision of de-capping robots in the table below, plus automation of results transcription to MatchPoint additional capacity of approximately 17,800 additional tests can be achieved per year (Table 8).

Table 8. Australian laboratory capability requirements for processing of buccal swab samples above current blood sample testing process for HLA typing

State	Additional buccal swabs per week (year)	Additional FTE to process additional samples	De-capping robot/ or additional robot for processing	Sequencer(s) capacity
SA	15 (800)	0.5	Not applicable	Yes
VIC	100 (5000)	2	1-2	Yes
NSW	100 (5000)	2	1	Yes
WA	100 (5000)	1	Not required	Yes
QLD	40 (2000)	-	1	
Total	355 (17,800)	5.5	3-4	

New testing platforms that could be utilised to identify potential HPC donor recruits

Lifeblood (Queensland) is currently validating a UBDT platform that will enable high-throughput NGS of all new blood donors, testing for red blood cell antigens, platelet antigens and HLA (see Figure 3). The level of resolution of HLA testing using the UBDT is sufficient for blood and platelet transfusion purposes (2-field resolution), but not sufficient for HPC transplantation decision-making. However, the UBDT provides a basis for increasing the pool of platelet donors and HPC donors from among the existing pool of blood donors, via identifying individuals from the blood donor pool who may have rare or under-represented HLA subtypes. Upon counselling and with informed consent, these donors

could subsequently progress to high resolution HLA testing to determine their suitability for platelet or HPC donor registration.

Proposed changes to the HPC donor recruitment target and recruitment method

HPC donor recruitment should continue to be a voluntary activity, undertaken with appropriate informed consent and that individuals may withdraw at any time, without coercion. Payment should continue to only be made for (incidental) expenses if a HPC recruit is called upon to donate. However, it is recognised that if there are barriers to donation; the donor might need to take unpaid leave to provide a HPC donation, which is a concern for those in short-term employment. Whilst the payment of expenses was not in the specific remit of the Advisory Group, the JHPCC should consider options to minimise the risk of HPC recruits declining to donate once called upon.

Although the recommendation to increase the target for HPC donor recruitment will increase the likelihood of finding suitably HLA matched Australian donors for Australian and overseas recipients, complete self-sufficiency is not possible. There will continue to be reliance on international registries to identify an appropriate overseas donor for many Australian recipients.

An absolute increase in recruitment numbers *and* an ongoing demonstration of increasing ancestry and HLA diversity among recruits following the proposed changes in recruitment activities is required, through an annual review to inform optimal recruitment strategies, discussed below.

The comparative age-range for HPC donor recruitment in other countries was considered, noting the variation in upper age limit. Given the need to increase ethnicity and HLA diversity of the national registry, it was considered on balance more prudent to widen the age range eligibility at recruitment now.

Activities to increase HPC donor recruitment should not be at the expense of the recruitment of Australian blood donors in maintaining the domestic supply of blood and blood-related products, aiming to arrest demand for more costly imported products.

The Advisory Group recommends achieving the increase and expansion of HPC donor recruitment through a combination of Lifeblood *and* ABMDR activity:

- (i) increasing Lifeblood testing capacity to enable a higher proportion of existing and new Lifeblood blood donors to become HPC recruits (using blood-based HLA, blood group and CMV testing). This will have a flow-on benefit for identifying additional platelet donors.
- (ii) HPC donor recruitment through fixed or mobile Lifeblood centres using a combination of initial buccal swab (for HLA) and later blood testing (for blood group and CMV).
- (iii) ABMDR-led, directed face-to-face community recruitment using only buccal swab testing (i.e. not via a Lifeblood centre)
- (iv) ABMDR-led online community recruitment using only buccal swab testing (i.e. not via a Lifeblood centre)

Based on the cumulative population identified as 'diverse' (through self-reported assignment) in the STG pilot programs, the estimated size of ongoing recruitment of the most diverse populations is approximately 57,000 individuals over five years. Such recruitment would likely benefit most from face-to-face recruitment which would likely need facilitation through community engagement.

Regular post-recruitment contact with all recruits should occur to ensure ongoing willingness to donate if called upon; those voluntarily withdrawing should be to be removed from the register in a timely manner.

Appendix 1:

Testing performed on recruitment samples by international HPC donor registries

Summary of testing performed on buccal swab or blood samples at recruitment by international HPC donor registries (updated March 2023)

Country	Registry Name	Recruitment sample type	Routine level of HLA typing	Capability to perform HLA typing (Verification typing vs Extended Typing) Level of HLA typing	At recruitment (swab)			Routine verification typing (blood or swab)	Target Age at recruitment	Retirement age from register
					HLA Testing	ABO	CMV			
Australia	ABMDR	Blood draw (3 tubes for new donor) (1 tube for existing blood donor)	<u>Lifeblood</u> 6 loci (HLA-A, HLA-B, HLA-C, DQB1, DPB1, DRB1) at 3 field or higher resolution using NGS	<u>Lifeblood</u> Capability for typing at 11 loci at 3-4 field level resolution	Yes	Yes	Yes	Blood	18-45 years up to 2018, most recent STG website update (Sep 2022) states 18-35 years	61 years
	ABMDR Strength to Give Pilot 1 (self-funded)	4 x swabs (not listed on ARTG)	6 loci (HLA-A, HLA-B, HLA-C, DPB1, DRB1 and DQB1) at 3-2 field G codes using NGS through Histogenetics (USA)	unknown	Yes*	Yes*	Yes*	Blood	18-30 years (based on social media posts during pilot)	
	ABMDR Strength to Give Pilot 2 (government funded)	3 x nylon tipped FLOQSwab (listed on ARTG)	6 loci (HLA-A, HLA-B, HLA-C, DPB1, DRB1 and DQB1) at 3 fields or higher using NGS.	<u>Pathwest</u> have capability for 11 loci via NGS	Yes	Yes*	Yes*	Blood	18-35 years (based on social media posts during pilot)	
United Kingdom	<u>Anthony Nolan</u> ²⁹	Swab (2 swabs for HLA ³⁰)	Allelic level typing at 9 loci (HLA- A, HLA-B, HLA-C, DRB1, DRB3/4/5, DQB1 and	Capability for 11 loci	Yes	Yes	Yes	unknown	Must be 16-30 years	Until 61 years old

²⁹ Source: Review of international best practice in HPC donor recruitment and retention, PwC 6 July 2021

³⁰ Anthony Nolan UK – Histocompatibility Laboratories, Service Provision User Guide, Version 10.0 – Access “Laboratory Users guide” via <https://www.safetyandquality.gov.au/publications-and-resources/resource-library/requirements-medical-testing-human-genetic-variation-third-edition>

			DPB1) with additional results for DQA1 and DPA1, where possible.							
	<u>British Bone Marrow Registry</u> Recruitment from UK blood donors	Blood sample	High resolution typing using NGS since 2015/16 ³¹	Expect capability matches Anthony Nolan	Yes	Yes	Yes	Blood	17-40 years	60 years
Singapore	<u>Bone Marrow Donor Programme (BMDP)</u> ²⁹	Swabs			Yes	unknown	unknown	Blood	Must be 18-49 years	Until 60 years old
United States	National Marrow Donor Program (NMDP) operates through Be The Match ²⁵	Nylon swabs ²⁵ 2 swabs ³² in kit Cotton swab kits from LabCorp ³³	High resolution using Next-Generation Sequencing (NGS)	unknown	Yes	Yes	Yes	Swabs	Must be 18-40 years old	61 years ³⁴
	<u>Gift of Life</u>	Swabs (donors use 4 swabs ³⁵)	Unknown		Yes	unknown	unknown	Blood and includes infectious disease markers ³⁶	Must be 18-35 years inclusive. Those aged 36-60 years pay test cost to join	Until 61 years old

³¹ NHSBT first in UK to use Next Generation Sequencing - NHS Blood Donation - [https://www.blood.co.uk/news-and-campaigns/news-and-statements/nhsbt-first-in-uk-to-use-next-generation-sequencing/#:~:text=In%202015%2F16%20NHS%20Blood%20and%20Transplant%20aims%20to,times%20more%20likely%20to%20be%20selected%20for%20transplant.](https://www.blood.co.uk/news-and-campaigns/news-and-statements/nhsbt-first-in-uk-to-use-next-generation-sequencing/#:~:text=In%202015%2F16%20NHS%20Blood%20and%20Transplant%20aims%20to,times%20more%20likely%20to%20be%20selected%20for%20transplant.https://bethematch.org/swabguide/)

³² <https://bethematch.org/swabguide/>

³³ Yin, Y. *et al.*, Application of High-Throughput Next-Generation Sequencing for HLA Typing on Buccal Extracted DNA: Results from over 10,000 Donor Recruitment Samples, PLoS One, 2016 Oct; 11(10) <https://doi.org/10.1371/journal.pone.0165810>

³⁴ <https://bethematch.org/transplant-basics/matching-patients-with-donors/why-donor-age-matters/>

³⁵ [Learn, Swab, Save Lives - Gift of Life -](https://www.giftoflife.org/donors/donationprocess1#:~:text=The%20swab%20kit%20is%20processed%20at%20Gift%20of,system%20factors%20used%20to%20match%20donors%20and%20recipients.https://www.giftoflife.org/donors/donationprocess2)

[https://www.giftoflife.org/donors/donationprocess1#:~:text=The%20swab%20kit%20is%20processed%20at%20Gift%20of,system%20factors%20used%20to%20match%20donors%20and%20recipients.](https://www.giftoflife.org/donors/donationprocess1#:~:text=The%20swab%20kit%20is%20processed%20at%20Gift%20of,system%20factors%20used%20to%20match%20donors%20and%20recipients.https://www.giftoflife.org/donors/donationprocess2)

³⁶ Gift of Life Confirmatory Typing accessed from: <https://www.giftoflife.org/donors/donationprocess2>

Germany	<u>Deutsche KnochenMarkSpenderdatei (DKMS)</u> ^{29, 37}	FLOQSwab (nylon)	11 loci at high resolution (HLA-A, HLA-B, HLA-C, DQB1, DPB1 DRB1) or 11 loci (exons 2 and 3)	Capacity for 11 loci (at high resolution) although it is not routine for donor registration	Yes	Yes	Yes	Blood	Must be 17-55 years. At 18 years, younger registrants become available on searches.	unknown
Canada	<u>Canadian Blood Services Stem Cell Registry (formerly known as OneMatch)</u> ²⁹	Blood draw or swabs (donors use 4 swabs ^{38, 39})			Yes	Yes	Yes	Unknown	Preferably 17-35 years	Up to 60 years old ⁴⁰
	<u>Hema-Quebec Stem Cell Donor Registry</u>	4 x swabs	Low-resolution (by SSO) and high-resolution (by NGS) HLA typing for HLA-A, -B, -C, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1 and DPB1 loci		Yes	Unknown	Unknown	Blood	18-35 years old	Up to 60 years old

* Testing performed overseas by Histogenetics <https://www.histogenetics.com/>

- All registries consulted in Australia and overseas for the PwC Reviews, can perform full gene typing (11 loci) at high resolution.
- CMV tests on buccal swabs – overseas registries accept that CMV status from buccal swabs are not diagnostic tests, and therefore accept lower sensitivity for CMV detection for donor registration

³⁷ DKMS is an international charity with donor centres in Childe, Poland, UK, United States, India and Africa, information listed relates to the registry based in Germany.

³⁸ Fingrut *et al.* (2020) Targeted recruitment of optimal donors for unrelated hematopoietic cell transplantation: The Stem Cell Club process, Hematology/Oncology and Stem Cell Therapy; 13(4):220-231, <https://doi.org/10.1016/j.hemonc.2020.04.001>

³⁹ Stem Cell Registration – Buccal Swab, Canadian Blood Services, <https://www.youtube.com/watch?v=lrOis-F3CiE>

⁴⁰ <https://www.blood.ca/sites/default/files/1000106075.pdf>