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FEATURE

Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019

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Abstract

This is the seventh special EBMT report on the indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders. Our aim is to provide general guidance on transplant indications according to prevailing clinical practice in EBMT countries and centres. In order to inform patient decisions, these recommendations must be considered together with the risk of the disease, the risk of the transplant procedure and the results of non-transplant strategies. In over two decades since the first report, the EBMT indications manuscripts have incorporated changes in transplant practice coming from scientific and technical developments in the field. In this same period, the establishment of JACIE accreditation has promoted high quality and led to improved outcomes of patient and donor care and laboratory performance in transplantation and cellular therapy. An updated report with operating definitions, revised indications and an additional set of data with overall survival at 1 year and non-relapse mortality at day 100 after transplant in the commonest standard-of-care indications is presented. Additional efforts are currently underway to enable EBMT member centres to benchmark their risk-adapted outcomes as part of the Registry upgrade Project 2020 against national and/or international outcome data.

Introduction

This manuscript is the seventh report from the European Society for Blood and Marrow Transplantation (EBMT) on the indications for haematopoietic stem cell transplantation (HSCT) according to prevailing clinical practice in EBMT countries and centres [1–6]. As in previous editions, the recommendations 2019 are based on clinical trials, registry data and the opinion from EBMT experts from the relevant working parties but not on a formal extensive review of the literature. They aim to provide general guidance on transplant indications, and in order to inform patient decisions, they must be considered together with the risk of the disease, the risk of the transplant procedure and the results of non-transplant strategies. Besides a possible survival gain, this assessment must include issues of quality of life and late effects, which are particularly important in children and adolescents. The recommendations are not meant to decide on the use of a particular transplant protocol, conditioning regimen or stem cell source. In over two decades since the first report, the EBMT indications manuscripts have incorporated changes in HSCT practice coming from scientific and technical developments in the field as well as in other non-transplant treatment strategies. In this same period, the establishment of the Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and the EBMT–JACIE, the standards of which were first approved by the EBMT General Assembly in March 1998, has promoted high quality and improved outcomes of patient and donor care and laboratory performance in HSCT and cellular therapy. Additional efforts are currently

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underway as part of the Registry upgrade Project 2020 to implement the statistical methodology that will enable EBMT member centres to benchmark their survival outcomes against national and/or international outcome data.

Transplant categorisation, definitions and factors

Haematopoietic stem cell transplant

HSCT refers to any procedure where haematopoietic stem cells of any donor type and any source are given to a recipient with the intention of repopulating and replacing the haematopoietic system in total or in part. Stem cells for HSCT can be derived from bone marrow (BM), peripheral blood (PB) or cord blood (CB).

Donor categories and stem cell sources

Donor type is categorised as autologous, syngeneic and allogeneic, the latter being either related or unrelated. Beyond HLA-matched related (i.e. sibling) donors (MSD), a well-matched unrelated donor (MUD) is defined as a 10/10 or 8/8 identical unrelated donor based on HLA high-resolution typing for class I (HLA-A, -B, -C) and II (HLA-DRB1, -DQB1). A mismatched unrelated donor (MMUD) refers to an adult unrelated donor mismatched in at least one antigen or allele at HLA-A, -B, -C, or -DR. Of note, not all HLA mismatches are equal. Permissive HLA mismatches can be tolerated with outcomes similar to those from well-matched donors, but non-permissive HLA allele mismatch combinations lead to poorer outcomes [7–11]. Improved categorisation of HLA matching status in the context of incomplete HLA characterisation in international registries has identified an additional category of partially matched HLA donor–recipient pairs, defined as those with a defined single-locus mismatch and/or missing HLA data, which allows adjustment of donor–recipient HLA compatibility for retrospective analyses, but this is not applicable to prospective donor selection [12]. In this setting, other genetic factors, such as killer cell immunoglobulin-type receptors [13], can aid in the selection of potentially better unrelated donors. Such novel criteria for donor selection are beyond the scope of these recommendations and their potential incorporation into clinical practice will depend on the effort from donor registries and transplant centres as much as on the further development of strategies to incorporate mismatched alternative donors (MMAD) into practice.

In the previous EBMT indications manuscript, we described in some detail the assessment of comorbidities and risk prior to HSCT, the use of reduced-intensity conditioning protocols in older transplant candidates, the choice of stem cell source for autologous and allogeneic HSCT and the relative preference of using PB stem cells or BM in the setting of high-risk malignant versus non-malignant indications in relation with the occurrence of chronic graft-versus-host disease (GVHD). We also discussed the value of CB as a stem cell source for allogeneic HSCT from MMAD, including strategies to facilitate and accelerate engraftment, as well as the start of an increasing trend to use haploidentical family donors, as their practical advantages in terms of availability and low cost met the use of high-dose posttransplant cyclophosphamide, which is a reproducible strategy to control their major drawback of strong alloreactive responses between donor and recipient. As a thorough revision of these points would be beyond the scope of this new report, for them we refer the reader to the previous EBMT indications manuscript [6].

An important conclusion from our previous report was that transplant physicians with allogeneic HSCT candidates lacking a well-matched related or unrelated donor back in 2015 faced a difficult technical decision to select the best MMAD among the various options available, which included MMUD, unrelated CB and haploidentical transplants [6]. Interestingly, 4 years later, now in 2019, that difficult decision remains far from settled. Top leaders in the field recognise that, despite some clear advantages and disadvantages for the various options available, we still do not to know which should be the best alternative to MSD for most patients, in a debate that remains open to this date [14–17]. Some groups would suggest that some MMAD should be preferred for particular indications, such as for instance CB for high-risk acute myeloid leukaemia (AML) with minimal residual disease detectable at the time of HSCT [18]. In terms of transplant activity, however, the past few years have witnessed a very significant reduction in the use of CB and an exponential expansion in the use of haploidentical donors [19–22], which in the most recent EBMT activity survey represent a total of 368 CB (2.0%) and 2684 haploidentical donors (14.7%) out of 18,200 allogeneic HSCT reported in 2017 [23]. Transplant decisions and trends derive not only from sound scientific evidence but also from each centre's research priorities, local expertise, cost considerations and easiness of access to particular transplant modalities. However, in the absence of strong evidence in terms of survival benefit, we combine the recommendations for MMAD, including CB, haploidentical and MMUD, in a single category separate from well-matched related and unrelated donors. Beyond this general approach to recommendations for MMAD HSCT, the relative value of the various modalities is described and addressed in more detail below in sections for the relevant indications.

Categorisation of type of indication for transplant procedures

EBMT indications are classified into four categories, listed below, to describe the settings where these types of transplants ought to be performed. The strength of the evidence supporting the assignment of a particular category is graded in three levels:

- Grade I: Evidence from at least one well-executed randomised trial.
- Grade II: Evidence from at least one well-designed clinical trial without randomisation; cohort or case-controlled analytic studies (preferably from more than one centre); multiple time-series studies or dramatic results from uncontrolled experiments.
- Grade III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports from expert committees.

Standard of care (S): Indications categorised as S are reasonably well defined and results compare favourably (or are superior) to those of non-transplant treatment approaches. Obviously, defining an indication as the standard of care does not mean an HSCT is necessarily the optimal therapy for a given patient in all clinical circumstances. Standard of care transplants may be performed in a specialist centre with experience in HSCT and an appropriate infrastructure as defined by the JACIE guidelines.

Clinical option (CO): The CO category applies to indications for which the results of small patient cohorts show efficacy and acceptable toxicity of the HSCT procedure, but confirmatory randomised studies are missing, often as a result of low patient numbers. The broad range of available transplant techniques combined with the variation of patient factors such as age and co-morbidity makes interpretation of these data difficult. Our current interpretation of existing data for indications placed in this category supports that HSCT is a valuable option for individual patients after careful discussions of risks and benefits with the patient but that for groups of patients the value of HSCT needs further evaluation. Transplants for indications under this heading should be performed in a specialist centre with major experience in HSCT with an appropriate infrastructure as defined by JACIE guidelines.

Developmental (D): Indications have been classified as D when the experience is limited, and additional research is needed to define the role of HSCT. These transplants should be done within the framework of a clinical protocol, normally undertaken by transplant units with acknowledged expertise in the management of that particular disease or that type of HSCT. Protocols for D transplants will have been approved by local research ethics committees and must comply with current international standards. Rare indications where formal clinical trials are not possible should be performed within the framework of a structured registry analysis, ideally an EBMT non-interventional/observational study. Centres performing transplants under this category should meet JACIE standards.

Generally not recommended (GNR): The GNR category comprises a variety of clinical scenarios in which the use of HSCT cannot be recommended to provide a clinical benefit to the patient, including early disease stages when results of conventional treatment do not normally justify the additional risk of a HSCT, very advanced forms of a disease in which the chance of success is so small that does not justify the risks for patient and donor and indications in which the transplant modality may not be adequate for the characteristics of the disease. A categorisation as GNR does not exclude that centres with particular expertise on a certain disease can investigate HSCT in these situations. Therefore, there is some overlap between GNR and D categories, and further research might be warranted within prospective clinical studies for some of these indications.

Transplant indications in adults

The updated 2019 classification of HSCT procedures in adults is shown in Table 1.

Acute myeloid leukaemia (AML)

AML is the most frequent indication for allogeneic HSCT in Europe, followed by acute lymphoblastic leukaemia (ALL) [19–23]. The most striking development in recent years has been in non-T-depleted haploidentical donor HSCT. Adult patients with AML should always be considered for HSCT, but the decision to proceed to HSCT should be based on the balance between the disease relapse risk and transplant-related mortality [24]. Major progress has been made in recent years in defining the acute leukaemia risk categories that includes not only white blood cell counts and response to induction therapy but most importantly also cytogenetics refined by molecular markers and somatic mutations [25, 26]. Similarly, risk scores and comorbidities are much better defined [27], and transplantation outcome has been significantly improved with reduction of about 50% in related mortality [28]. Patients with favourable prognosis AML, based on cytogenetics/molecular markers, such as patients with core binding factor leukaemia [t(8;21) or inv(16)], patients with biallelic gene

Table 1 Proposed classification of transplant indications for adults—2019

Disease	Disease status	MSD Allo	MUD Allo	MMAD Allo	Auto
Leukaemias					
AML	CR1 (favourable risk and MRD−)[a]	GNR/II	GNR/II	GNR/II	CO/I
	CR1 (favourable risk and MRD+)[a]	CO/II	CO/II	CO/II	GNR/II
	CR1 (intermediate risk)[a]	S/II	CO/II	CO/II	CO/I
	CR1 (adverse risk)[a]	S/II	S/II	S/II	GNR/I
	CR2	S/II	S/II	S/II	CO/II
	APL molecular CR2	S/II	CO/II	GNR/III	S/II
	Relapse or refractory	CO/II	CO/II	CO/II	GNR/III
ALL	Ph (−), CR1 (standard risk and MRD−)[a]	GNR/II	GNR/II	GNR/III	CO/III
	Ph (−), CR1 (standard risk and MRD+)[a]	CO/II	CO/II	CO/II	GNR/II
	Ph (−), CR1 (high risk)[a]	S/II	S/II	CO/II	GNR/III
	Ph (+), CR1 (MRD−)	S/II	S/II	CO/II	CO/III
	Ph (+), CR1 (MRD+)	S/II	S/II	S/II	GNR/II
	CR2	S/II	S/II	S/II	GNR/II
	Relapse or refractory	CO/II	CO/II	CO/II	GNR/III
CML	First CP, failing second- or third-line TKI	S/II	S/II	CO/III	GNR/II
	Accelerated phase, blast crisis or >first CP	S/II	S/II	CO/II	GNR/III
Myelofibrosis	Primary or secondary with an intermediate or high DIPSS score	S/II	S/II	S/III	GNR/III
MDS	RA, RCMD, RAEB I and II	S/II	S/II	S/II	GNR/III
	sAML in CR1 or CR2	S/II	S/II	S/II	CO/II
	More advanced stages	S/II	S/II	S/II	GNR/III
CLL	Poor risk disease, not transformed	S/II	S/II	CO/III	GNR/III
	Richter's transformation	S/III	S/III	CO/III	CO/III
Lymphoid malignancies					
DLBCL	CR1 (Intermediate/high IPI at dx)	GNR/III	GNR/III	GNR/III	CO/I
	Chemosensitive relapse, ≥CR2	CO/II	CO/II	D/III	S/I
	Chemosensitive relapse after auto-HSCT failure	S/II	S/II	CO/III	GNR/III
	Refractory disease	CO/II	CO/II	CO/III	CO/II
	Primary CNS lymphoma	GNR/III	GNR/III	GNR/III	S/I
FL	CR1, untransformed	GNR/III	GNR/III	GNR/III	GNR/II
	CR1, transformed to high-grade lymphoma	GNR/III	GNR/III	GNR/III	CO/III
	Chemosensitive relapse, ≥CR2	CO/III	CO/III	GNR/III	S/II
	≥CR2 after auto-HSCT failure	S/II	S/II	D/III	GNR/III
	Refractory	CO/II	CO/II	CO/III	GNR/III
MCL	CR1	GNR/III	GNR/III	GNR/III	S/I
	CR/PR > 1, no prior auto-HSCT	CO/III	CO/III	D/III	S/II
	CR/PR > 1, after prior auto-HSCT	S/II	S/II	CO/III	GNR/II
	Refractory	CO/II	CO/II	D/III	GNR/II
WM	CR1	GNR/III	GNR/III	GNR/III	GNR/III
	Chemosensitive relapse, ≥CR2	GNR/III	GNR/III	GNR/III	CO/II
	Poor risk disease	CO/II	CO/II	D/III	GNR/III

Table 1 (continued)

Disease	Disease status	MSD Allo	MUD Allo	MMAD Allo	Auto
PTCL	CR1	CO/II	CO/II	GNR/III	CO/II
	Chemosensitive relapse, ≥CR2	S/II	S/II	CO/III	CO/II
	Refractory	CO/II	CO/II	CO/III	GNR/II
Primary CTCL	EORTC/ISCL stages I–IIA (Early)	GNR/III	GNR/III	GNR/III	GNR/III
	EORTC/ISCL stages IIB–IV (Advanced)	CO/III	CO/III	D/III	GNR/III
HL	CR1	GNR/III	GNR/III	GNR/III	GNR/I
	Chemosensitive relapse, no prior auto-HSCT	D/III	D/III	GNR/III	S/I
	Chemosensitive relapse, after prior auto-HSCT	S/II	S/II	CO/III	CO/III
	Refractory	D/II	D/II	D/III	CO/III
MM	Upfront standard risk	CO/II	CO/II	GNR/III	S/I
	Upfront high risk	S/III	S/III	CO/II	S/I
	Chemosensitive relapse, prior auto-HSCT	CO/II	CO/II	CO/II	S/II
AL		CO/III	CO/III	GNR/III	CO/II
Other diseases					
Acquired SAA and	Newly diagnosed	S/II	CO/II	GNR/III	NA
AA/PNH	Relapsed/refractory	S/II	S/II	CO/II	NA
Haemolytic PNH		GNR/II	GNR/II	GNR/II	NA
Constitutional SAA[b]		S/II	S/II	CO/II	NA
Breast Ca	Adjuvant high risk, HER2 negative	GNR/III	GNR/III	GNR/III	CO/II
	Metastatic, chemosensitive	D/II	D/II	GNR/III	D/CO/II
Germ Cell Tumours	Second line, high risk	GNR/III	GNR/III	GNR/III	CO/II
	Primary refractory, second and further relapse	GNR/III	GNR/III	GNR/III	S/II
Ovarian Ca	High risk/recurrent	D/II	GNR/III	GNR/III	GNR/I
Medulloblastoma	Post-surgery, high risk	GNR/III	GNR/III	GNR/III	CO/III
Small cell lung Ca	Limited	GNR/III	GNR/III	GNR/III	D/II
Soft tissue Sa	Metastatic	D/III	GNR/III	GNR/III	GNR/II
Ewing's Sa	Locally advanced/metastatic, chemosensitive	D/III	GNR/III	GNR/III	CO/III
Renal cell Ca	Metastatic, cytokine-refractory	D/II	D/II	GNR/III	GNR/III
Pancreatic Ca	Advanced	D/III	GNR/III	GNR/III	GNR/III
Colorectal Ca	Metastatic	D/III	GNR/III	GNR/III	GNR/III
Multiple Sclerosis	Highly active RR-MS failing DMT	D/III	GNR/III	GNR/III	S/I
	Progressive MS with AIC, and aggressive MS[c]	D/III	GNR/III	GNR/III	CO/II
Systemic sclerosis		D/III	GNR/III	GNR/III	S/I
SLE		D/III	GNR/III	GNR/III	CO/II
Crohn's disease		D/III	D/III	D/III	CO/II
Rheumatoid arthritis		D/III	GNR/III	GNR/III	CO/II
JIA		CO/II	CO/II	CO/III	CO/II
Monogenic AD		CO/II	CO/II	CO/III	GNR/II
Vasculitis		GNR/III	GNR/III	GNR/III	CO/II
PM-DM		GNR/III	GNR/III	GNR/III	CO/II

Table 1 (continued)

Disease	Disease status	MSD Allo	MUD Allo	MMAD Allo	Auto
Autoimmune cytopenias		CO/II	CO/II	CO/III	CO/II
Neuromyelitis Optica		D/III	D/III	D/III	CO/II
CIDP, MG and SPS		GNR/III	GNR/III	GNR/III	CO/II
Type 1 diabetes		GNR/III	GNR/III	GNR/III	D/II
RCD type II		GNR/III	GNR/III	GNR/III	CO/II
Primary ID		CO/II	CO/II	CO/II	NA

AA aplastic anaemia, *AD* autoimmune disorders, *AIC* active inflammatory component, *AL* amyloidosis, *ALL* acute lymphoblastic leukaemia, *Allo* allogeneic transplantation, *AML* acute myeloid leukaemia, *APL* acute promyelocytic leukaemia, *Auto* autologous transplantation, *Ca* cancer or carcinoma, *CIDP* chronic inflammatory demyelinating polyneuropathy, *CLL* chronic lymphocytic leukaemia, *CML* chronic myelogenous leukaemia, *CNS* central nervous system, *CO* clinical option (can be carried after careful assessment of risks and benefits), *CP* chronic phase, *CR1, 2, 3* first, second, third complete remission, *CTCL* cutaneous T cell lymphoma, *D* developmental (further trials are needed), *DIPSS* Dynamic International Prognostic Score System, *DLBCL* diffuse large B cell lymphoma, *DMT* disease-modifying treatments, *FL* follicular lymphoma, *GNR* generally not recommended, *HL* Hodgkin lymphoma, *HSCT* haematopoietic stem cell transplantation, *ID* immunodeficiency, *IPI* International Prognostic Index, *JIA* juvenile idiopathic arthritis, *MCL* mantle cell lymphoma, *MDS* myelodysplastic syndromes, *MG* myasthenia gravis, *MM* multiple myeloma, *MMAD* mismatched alternative donors (cord blood, haploidentical and mismatched unrelated donors), *MRD* minimal residual disease, *MS* multiple sclerosis, *MSD* matched sibling donor, *MUD* well-matched unrelated donor (8/8, 10/10 or 9/10 if mismatched is in DQB1), *NA* not applicable, *PM-DM* polymyositis-dermatomyositis, *PNH* paroxysmal nocturnal haemoglobinuria, *PR* partial remission, *RA* refractory anaemia, *RAEB* refractory anaemia with excess blasts, *RCD* refractory coeliac disease, *RCMD* refractory cytopenia with multilineage dysplasia, *RR-MS* relapsing–remitting multiple sclerosis, *S* standard of care (generally indicated in suitable patients), *Sa* sarcoma, *SAA* severe aplastic anaemia, *sAML* secondary acute myeloid leukaemia, *SLE* systemic lupus erythematosus, *SPS* stiff person syndrome, *TCL* T cell lymphoma, *TKI* tyrosine kinase inhibitors, *WM* Waldenström macroglobulinemia. This classification does not cover patients for whom a syngeneic donor is available

[a]Categories are based on number of white blood cells, cytogenetics and molecular markers at diagnosis and time to achieve remission (see text)

[b]Constitutional SAA include Fanconi anaemia, dyskeratosis congenita, Blackfan–Diamond anaemia and other inborn bone marrow failure syndromes (see also the section and table for paediatric indications)

[c]Aggressive MS as per [275]

mutation in the CCAAT/enhancer binding protein α gene (CEBPA) and patients with mutation in NPM1 but no Flt3-ITD [26, 29], should now be evaluated for consolidation with an autologous HSCT in first complete remission (CR1) if in molecular remission and with no disease marker detectable in the leukapheresis product and may also be considered for an allogeneic HSCT in case of positive measurable residual disease (MRD) [30]. Supporting evidence comes as well from EBMT studies [31], and meta-analysis of several randomised studies on 2983 patients analysed for CEBPA mutational status [32], which showed that relapse-free survival was significantly superior in patients receiving an allogeneic HSCT or an autologous HSCT in CR1 as compared with chemotherapy ($p < 0.001$), with a trend for a better overall survival (OS). The use of MMAD and MUD is constantly increasing in such patients due to continuous improvement of outcome results [33, 34]. These indications continue to be refined in many centres based on the evaluation of MRD prior to allogeneic HSCT. Finally, patients from the favourable risk group, who do not achieve CR1 after one well-conducted induction course, should also be considered to proceed to allogeneic HSCT using the best available donor.

Patients from the adverse risk category (2017 European Leukaemia Network recommendations) [26] in CR1 should be allografted with the best available donor including HLA-identical family members, unrelated donors, haploidentical donors and CB, as part of a standard-of-care approach. Autologous HSCT is not recommended here [35, 36]. Other patients in CR1 who belong to the intermediate-risk category are candidates for allogeneic HSCT using mainly HLA-identical sibling donors or well-matched HLA unrelated donors. Autologous HSCT has recently also regained interest in these patients [37]. Patients with AML M3 achieving CR2 and MRD negativity should be autografted (S), since the outcome is similar or better than after allogeneic transplantation [38–41].

Acute lymphoblastic leukaemia

The field of adult ALL is facing major progress with the introduction of paediatric-type chemotherapy protocols and MRD monitoring, as well as novel monoclonal antibodies and innovative cellular therapies such as chimeric antigen receptor (CAR)-T cells. Of note, the vast majority of patients with adult ALL can have molecular targets

identified for MRD assessment, and MRD can be measured at different times in the disease and potentially identify different risk groups. However, one should bear in mind that MRD relevance at any time point is dependent on specific prior therapy and possibly cannot be extrapolated from one protocol to another [42]. From this progress, allogeneic HSCT is not systematically proposed to standard risk ALL [43], especially in MRD-negative patients. However, it remains the standard of care in high-risk patients such as slow remitters, steroid and/or chemotherapy-resistant patients, and all patients following relapse following CR1.

A large meta-analysis using data from 13 studies including 2962 patients [44], excluding Philadelphia chromosome (Ph)-positive (Ph+) patients, showed a survival benefit for patients <35 years of age with a matched sibling donor (odds ratio (OR) = 0.79, $p = 0.0003$) but not for older patients (OR = 1.01, $p = 0.9$) for their higher risk of non-relapse mortality. No beneficial effect of autografting was seen compared with chemotherapy in this analysis. Allogeneic HSCT is a standard of care for patients with Ph+ ALL. The introduction of tyrosine kinase inhibitors (TKIs) to first-line therapy has improved overall outcomes; however, a significant proportion of patients still relapse, even after HSCT. Post-transplant TKI maintenance associated with a reduced risk of relapse in a large retrospective study and therefore should be considered a valuable option [45]. Higher-risk adult patients with ALL and persistent or relapsing MRD are candidates for allogeneic HSCT in CR1 using the best available donor. Patients relapsing after chemotherapy and achieving CR2 are also candidates for allogeneic HSCT using the best available donor. Autologous HSCT is a clinical option for patients with either Ph+ or Ph-negative ALL and negative MRD. However, it is generally not recommended for all other cases of higher-risk ALL.

The arrival of CAR-T cells targeting CD19 has shown impressive results in patients with advanced forms of ALL, including relapsed/refractory cases occurring after allogeneic HSCT. The use of CAR-T cells may turn in a true revolution for some patients affected with relapsed/refractory ALL and other severe or poor prognosis malignancies, as discussed in other indications below. EBMT and other societies and professional groups are making efforts to deliver a roadmap to implement CAR-T programmes that overcome potential limitations, secure good assessment and prediction of efficacy, manage toxicities for safe early delivery and long-term monitoring, as well as discuss with key stakeholders in order to improve accessibility and sustainability for healthcare programmes [46–50]. Additional experience will be needed with these new cellular therapies to decide on their optimal use, overall and with regards to their positioning in relation to the current standard of care of HSCT in many patients, as a potential bridge-to-transplant or in other clinical scenarios. Therefore, this report does not yet provide specific recommendations about the use of CAR-T cells in relation to HSCT in ALL or in other indications.

Chronic myeloid leukaemia (CML)

Since the advent of TKIs, allogenic HSCT is not recommended as first-line treatment after diagnosis of CML. Imatinib in the vast majority of CML patients in chronic phase or second-generation TKIs such as dasatinib, nilotinib or bosutinib should be the first-line therapy. Some patients in molecular remission after treatment with TKIs have remained in molecular remission for a long period after cessation of the drug and complete discontinuation of TKIs could be obtained in about 40% of those patients but it remains to be seen in the long term if those patients are cured [51, 52]. Patients who fail first-line therapy according to the European Leukaemia Net guidelines should start on second-line TKI therapy. Patients who fail two lines of TKI should start a search for a suitable related, unrelated or alternative donor as early as possible. They should receive treatment with third-line TKI depending on ABL mutation analyses and are candidates to proceed to HSCT in optimal response as soon as possible if their EBMT risk score is 0–1 or in case of a prior loss of cytogenetic or haematological response to second-line TKI if their EBMT risk score is 0–4. If there is no haematological response to second-line treatment, patients are candidates to allogeneic HSCT on any EBMT risk score. Patients with ABL mutations resistant to third-generation TKI or with the T315I mutation are candidates to undergo HSCT on any EBMT risk score after failing second- or third-line TKI. Patients in advanced phase referred for a HSCT could have therapy with TKI or intensive therapy ± TKI as preparation for HSCT, which should be performed as soon as possible after achieving second chronic phase without the need for deep cytogenetic or molecular responses. A patient with a syngeneic donor is always a candidate for a HSCT with standard conditioning. Autologous HSCT is generally not recommended outside clinical trials.

Myeloproliferative disorders other than CML

Allogeneic HSCT remains the only potential curative option for patients with myeloproliferative disorders. However, polycythaemia vera and essential thrombocythaemia are in general not indications for allogeneic HSCT, unless the disease has progressed to myelofibrosis or secondary leukaemia [53, 54]. Owing to lack of alternative therapeutic options, allogeneic HSCT is a reasonable treatment for primary myelofibrosis with intermediate II and high risk according to the Dynamic International Prognostic Index

[55]. In younger patients, transplantation in intermediate I is justified in individual cases, especially if unfavourable mutations such as EZH2 or ASXL1 or unfavourable cytogenetics are present [56, 57], but the allotransplant experience in low-risk index is limited and remains controversial. The available data do not support systematic splenectomy prior to HSCT. The introduction of JAK inhibitors in the treatment of myelofibrosis may help to improve constitutional symptoms and to reduce spleen size before transplantation, but its definitive role needs to be determined [58]. Autologous HSCT is generally not recommended outside clinical trials.

Myelodysplastic syndromes (MDS)

Allogeneic HSCT is the treatment of choice for adult patients with MDS or AML evolved from MDS, to whom it offers a good chance of long-term disease-free survival if the treatment is performed before disease progression or in CR after chemotherapy. The introduction of reduced-intensity conditioning regimens, extending the indication to older patients with comorbidities or reduced fitness, and the increasing use of unrelated or mismatched family donors have both contributed to the increasing activity and use of allogeneic HSCT in patients with MDS [59]. The International Prognostic Score System (IPSS) or the revised IPSS are valuable tools to assess a patient's prognosis without HSCT. Additional prognostic factors to be considered include marrow fibrosis, multilineage dysplasia, refractory cytopenia, transfusion requirement and somatic mutations [60–63]. The results of allogeneic HSCT seem to be better if the blast count does not exceed 5% at the time of transplant. Thus, in patients with excess blasts, intensive chemotherapy or hypomethylating agents are regularly used before transplant even though they have not been proved by controlled prospective studies to improve post-transplant outcome. The decision to proceed with allogeneic HSCT should be based on the risk of the disease and the risk of the transplant procedure estimated by the EBMT risk score and patient-related factors such as comorbidities, in keeping with international guidelines by the EBMT Chronic Malignancies Working Party [64].

Chronic lymphocytic leukaemia (CLL)

The introduction of signalling pathway inhibitors (PI), such as the Bruton's TKI ibrutinib, the phosphatidylinositol-3-kinase inhibitor idelalisib or the BCL2-inhibitor venetoclax, has changed CLL management algorithms and transplant indications. EBMT and ERIC (European Research Initiative in CLL) have recently proposed a revised definition of high-risk CLL driven by TP53 abnormalities and response to treatment with PI [65]. Patients with chemoimmunotherapy-resistant CLL but fully responsive to PI (high-risk I) should be treated with these drugs, and allogeneic HSCT remains an option only in selected patients with low procedure-related risk. Patients with CLL resistant to both chemoimmunotherapy and PI (high-risk II) have exhausted their main pharmacological therapeutic options and should be considered for cellular therapies, including CAR-T cells and allogeneic HSCT, if eligible. Of note, cellular and molecular therapies are not mutually exclusive and could be used synergistically to exploit their full potential. Finally, patients with CLL and a concomitant MDS and those with clonally related aggressive transformation of CLL should be considered for allogeneic HSCT regardless of the treatment stage of their CLL [66]. Autologous HSCT should be considered as a clinical option in patients with a histological transformation, which is clonally unrelated to CLL [66] but is generally not recommended in CLL otherwise.

Lymphomas

In December 2015, a new version of the mandatory MED-A standard reporting form became effective. Regarding lymphoma, the most important improvement was that the former CR1 is now split into two categories, allowing for the first time differentiating "true" CR1 (i.e. achievement of first CR directly by standard first-line treatment) from a "first" CR, which was achieved by one or more salvage attempts after primary induction failure. These two categories clearly segregate courses with different prognosis in each individual lymphoma subset. In the present edition, the recommendations listed in Table 1 always refer to "true" CR1 if CR1 is mentioned. In contrast, CR1 after prior refractoriness is regularly included in CR > 1 categories for the purpose of these recommendations. As a consequence, in some lymphoma entities transplant indications in CR1 are more restrictive now than in previous editions of these recommendations.

Diffuse large B-cell lymphoma (DLBCL)

Autologous HSCT remains the standard of care for patients with chemosensitive relapse of DLBCL after first-line therapy including rituximab, and allogeneic HSCT remains the standard of care for chemosensitive relapse after failure of a prior autograft [67–72]. Other recommendations, including the role of autologous HSCT as consolidation after rituximab-containing first-line therapy, or the roles of both autologous and allogeneic HSCT in high-risk relapsed or refractory DLBCL remain for now clinical options that need to be defined more clearly by further studies.

New recommendations for primary lymphoma of the central nervous system (CNS) have been introduced. In this DLBCL subset, there is evidence from a number of non-comparative trials and one randomised controlled trial that

consolidating autologous HSCT in first remission is safe and effective, justifying categorisation as S/II [73, 74]. In contrast, there is virtually no data on the efficacy of allogeneic HSCT in this setting, and therefore, it is generally not recommended.

Uncontrolled trials of CAR-T cellular therapy have shown high efficacy in patients with heavily pre-treated, relapsed and refractory DLBCL [75, 76], and two anti-CD19 constructs have been approved in Europe and the US for this indication. However, as previously described in ALL, further experience and results from comparative studies will be required before they can be included on transplant recommendations for DLBCL.

Follicular lymphoma (FL)

In the era of antibody maintenance, evidence for benefit of HSCT in CR1 is lacking in patients with untransformed FL and in those with high-grade transformation who have not received systemic treatment for the underlying FL before histological transformation. In contrast, consolidation with an autologous HSCT might be a clinical option in patients with chemosensitive high-grade transformation of a FL, if they had received prior systemic treatment for FL, especially if it included immunochemotherapy. Beyond the potential efficacy of CAR-T cellular therapy in FL, novel drugs including idelalisib have not changed the natural history of the disease, and transplant indications for FL beyond CR1 remain unchanged compared to the previous edition [6, 77].

Waldenström's macroglobulinemia (lymphoplasmacytic lymphoma with IgM gammopathy; WM)

With the advent of more effective novel agents for WM, such as rituximab, purine analogues, proteasome inhibitors and kinase inhibitors, strategies using first-line autologous HSCT in this indication are increasingly questionable and should not be recommended outside clinical trials [78]. Autologous HSCT should be considered as clinical option in first relapse and for patients requiring more than one line of therapy to achieve response [79, 80]. Also, allogeneic HSCT has been advocated as a clinical option for younger individuals with WM with an aggressive clinical course or high-risk disease according to the IPSS [78, 81]. Although a clear definition of aggressive WM is missing, allogeneic HSCT might be considered in patients with short-lived responses or refractory to chemoimmunotherapy, proteasome-based treatment and/or kinase inhibitors.

Mantle cell lymphoma (MCL)

Since our previous EBMT indications manuscript [6], ibrutinib has been approved as an effective salvage treatment for patients with relapsed or refractory MCL. However, a randomised trial has documented that the progression-free survival of relapsed MCL achieved with ibrutinib is still only modest [82]. Moreover, MCL prognosis after ibrutinib failure appears to be extremely poor [83]. Therefore, in contrast to CLL, in MCL the advent of targeted drugs, such as ibrutinib, has not yet significantly affected the natural course of the disease and thus transplant indications. On the other hand, ibrutinib might be beneficial for bridging patients with MCL to allogeneic HSCT [84]. Studies testing ibrutinib as part of first-line therapy are ongoing. Available evidence does not suggest benefit of allogeneic HSCT in MCL in CR1 [85]. Therefore, upfront allogeneic HSCT in MCL outside of clinical trials is not recommended.

T cell lymphomas

Peripheral T cell lymphomas usually carry a very poor prognosis. Allogeneic HSCT is effective in patients with relapsed and refractory disease and recommended as a standard of care in patients with chemosensitive relapse as the only curative modality in this condition. In CR1, however, since the previous edition of this manuscript, a prospective randomised trial testing the superiority of allogeneic over autologous HSCT had to be prematurely terminated owing to low likelihood of meeting its primary endpoint [86]. Thus both autologous and allogeneic HSCT are clinical options as consolidation of first response, but ongoing evaluation will be required to modify these recommendations further.

Primary cutaneous T cell lymphomas in early stage have an excellent outcome, and HSCT is generally not recommended. However, patients with EORTC/ISCL advanced stages IIB to IV have a dismal prognosis with conventional therapy [87–89]. Allogeneic HSCT offers these patients a clinically relevant and persistent graft-versus-lymphoma effect [90–92], which despite the lack of well-designed comparative trials, would suggest this to be an advantageous clinical option for these patients compared to their outcomes with only conventional therapy.

Hodgkin lymphoma (HL)

Targeted agents such as brentuximab vedotin and checkpoint inhibitors may shift the transplant algorithms for HL in the future. For now, as in previous recommendations, HSCT remains a standard of care for patients with relapsed HL chemosensitive to salvage therapy, autologous in those without a prior autograft and allogeneic HSCT in those after a failed prior autograft [93–97].

Multiple myeloma (MM)

The development of new agents for MM such as proteasome inhibitors (e.g. bortezomib, carfilzomib, ixazomib),

immunomodulatory drugs (e.g. thalidomide, lenalidomide and pomalidomide) and monoclonal antibodies (e.g. daratumumab) have led to big advances in the management of these patients and may eventually change the position of HSCT in this indication. Currently, first-line autologous HSCT is still the standard of care for newly diagnosed MM patients [98, 99]. Although best results are seen in patients achieving good responses prior to HSCT, some non-responding patients also benefit from this approach. Age should be considered in conjunction with the patient's general health and fitness. Total body irradiation should not be used in the conditioning regimen due to increased toxicity without appreciable benefit, and the addition of bortezomib or lenalidomide to conditioning regimen is yet to be proven to improve patient outcome [100]. Double autograft has been shown to be superior to one single autologous HSCT, although the benefit of the second transplant appears to be restricted to patients presenting with poor-risk features, not achieving CR or very good partial remission (PR) with the first transplant. High activity shown by immunomodulatory drugs and bortezomib before transplantation has led to their use as consolidation and maintenance therapies after autologous HSCT and may be an alternative option for these patients [101–104]. As the vast majority of patients still relapse after autologous HSCT, the use of a further autograft after re-induction therapy is an option and may be of particular benefit in patients achieving a long treatment-free interval of at least 18–24 months after transplant [105].

Allogeneic HSCT is a treatment with curative potential but is associated with considerable non-relapse mortality and might be used in selected high-risk patients [106]. The combination of autologous HSCT and reduced intensity conditioning allograft has shown survival benefit for high-risk patients, albeit inconsistently in various clinical trials [107–110]. Recently, allogeneic HSCT with post-transplant cyclophosphamide has been shown to be a feasible modality in MM, but relapse is still a problem [111]. Similarly to the autologous transplantation setting, new agents are complementary, non-redundant therapies and should be combined in the management of suitable allogeneic transplant candidates.

AL amyloidosis

Patients with systemic immunoglobulin-light-chain (AL) amyloidosis without severe heart failure benefit from high-dose therapy and auto-HSCT [112]. However, this benefit from autologous HSCT was not confirmed in a prospective randomised trial, which included patients with advanced cardiac amyloidosis [113]. Many recently published studies have reported an improved early mortality after appropriate risk assessment and consistently good hematologic responses and impressive long-term survival [114, 115]. In addition, cytogenetic aberrations like translocation t(11;14) can also guide therapy in AL amyloidosis [116]. Allogeneic HSCT might be considered as a clinical option in younger patients who relapsed or not responded after autologous HSCT and received at least one new drug (lenalidomide or bortezomib) [117].

Acquired severe aplastic anaemia (SAA)

HLA-identical sibling allogeneic HSCT is considered the standard of care for adult patients with SAA, although the outcome is worse in candidates over the age of 40 years [118–120]. In addition to age, a careful assessment of co-morbidities prior to HSCT should be made to determine fitness for upfront HSCT in the age group of 35–50 years. To reduce the risk of chronic GVHD, all patients should receive in vivo T cell depletion with ATG or alemtuzumab, and BM is the recommended source of stem cells [121–123]. Also, as conditioning regimen, young patients <30 years should receive high-dose cyclophosphamide (CY; 200 mg/kg) and those aged 30–50 years, a fludarabine-based regimen with lower-dose CY (120 mg/kg). There is no indication for using radiation in the conditioning for HLA-identical sibling HSCT.

Matched unrelated allogeneic HSCT is considered as first-line choice in young patients aged <18 years based on the excellent outcome compared to historical matched controls [124], provided that the transplant is feasible within the first 2 months after diagnosis. Alemtuzumab-based conditioning is also recommended [125]. If the interval to find a suitable MUD and proceed to HSCT is predicted to be longer, then immunosuppressive therapy with ATG (preferably with horse ATG) and cyclosporine A would be the recommended treatment choice. MUD HSCT in young and adult patients is indicated after failure to respond to one course of IST, normally assessed at 3–6 months. Age of recipient is also an issue for MUD HSCT and, along with assessment of comorbidities and other patient and transplant characteristics (e.g. CMV status, source of cells, use of ATG, interval diagnosis-transplant, HLA matching degree), should help evaluating patients who would benefit best from the procedure. Classically, patients up to 30 years within the first year from diagnosis are the best candidates for MUD HSCT. Otherwise, a non-transplant approach would be recommended (e.g. eltrombopag, androgens, second course of immunosuppressive therapy) [120, 122–128]. As in MSD HSCT, BM is the recommended stem cell source for MUD HSCT in SAA for ATG-based conditioning regimens. Studies are ongoing to determine whether there is any preferred stem cell source for alemtuzumab-based conditioning, which overall provides excellent results with durable engraftment and low incidence of chronic GVHD in older (>40 years) recipients of allogeneic HSCT for SAA

from MSD or MUD. Overall, we recommended to seek further advice from a SAA specialist centre.

Alternative donors for allogeneic HSCT (e.g. CB, haploidentical or MMUD) may be considered after failure to respond to immunosuppressive therapy in young patients up to 20 years of age in the absence of MSD or MUD [129–135]. The EBMT SAA Working Party has approved protocols for either CB and haploidentical HSCT in this indication.

Paroxysmal nocturnal haemoglobinuria (PNH)

As discussed in the previous edition of these recommendations, the introduction of anti-complement therapy with eculizumab changed the natural history of the disease, and allogeneic HSCT became generally not recommended for patients with haemolytic PNH for whom eculizumab is available. Potential indications remain dependent on the individual clinical manifestations of PNH: (i) AA/PNH syndrome, that is, PNH occurring in the presence of severe BM failure with a hypocellular BM (using the same criteria for SAA above for age, disease severity, timing of transplant, conditioning regimen and failure to respond to one course of immunosuppressive therapy in case of MUD HSCT) and (ii) clonal evolution of PNH to MDS/AML [136, 137]. Patients with poor response to eculizumab who remain severely transfusion dependent may be also considered for HSCT, depending on the availability of new complement inhibitors. If needed, expert advice should be sought from a PNH specialist centre.

Constitutional SAA

There is increasing awareness that constitutional SAA, including Fanconi anaemia, dyskeratosis congenita and other telomere diseases, may not only present in childhood but also in adults, often with more subtle clinical features. Allogeneic HSCT is the only treatment able to restore normal haematopoiesis in these patients. Transfusion-dependent Fanconi anaemia patients with a suitable allogeneic donor should be transplanted while in the phase of moderate cytopenia with no poor-risk clonal abnormalities and no MDS/AML [138, 139]. Although outcomes are reported to be better at age <10 years, this is not the only criteria to rely on for treatment decision making. Details on transplant conditioning for particular indications are beyond the scope of these recommendations, but it is important to stress here that standard doses of chemotherapy and/or irradiation should be absolutely avoided in HSCT for Fanconi anaemia due to the underlying defect in DNA repair. Although radiation-free regimens including busulphan, cyclophosphamide, fludarabine and ATG with the infusion of a T cell-depleted graft provide excellent outcomes in HSCT from allogeneic donors other than HLA-identical siblings [140], the addition of low-dose irradiation may be indicated for those patients with clonal evolution or receiving transplantation from an unrelated donor due to a higher risk of graft rejection. In addition, HLA-identical siblings, which are the donors of choice, must be tested for chromosomal fragility, given the fact that some Fanconi anaemia subjects can have nearly normal somatic and haematological phenotype. Finally, BM stem cells are recommended above PB stem cells, as the latter are an independent risk factor for second malignancies. A recent large retrospective SAA Working Party study on allogeneic HSCT for Dyskeratosis Congenita and other telomeropaties showed that pre-transplant organ damage (lung and liver) was associated with poorer outcome [141], suggesting that pre-transplant organ assessment should be a requirement for eligibility of the patient for HSCT. In this setting, reduced-intensity conditioning regimens incorporating fludarabine are currently recommended [142, 143]. As in Fanconi anaemia, potential sibling donors should be tested for telomere length and for mutations of gene of the telomerase–shelterin complex, to rule out those with alterations despite normal somatic and hematologic phenotype. For all these reasons, discussion with a specialist centre is advised regarding possible HSCT in these patients.

Solid tumours

At present, the EBMT Registry includes about 60,000 HSCT procedures in >42,000 patients with solid tumours, with >10,000 procedures performed in the last 5 years. On the other hand, with the possible exception of selected patients with germ cell tumours, breast cancer, Ewing's sarcoma and medulloblastoma, HSCT is generally not recommended or developmental for most indications in solid tumours [6]. Despite the encouraging role of immune surveillance and immune responses against some solid tumours [144–146], such as renal cell carcinoma and melanoma, recommendations for allogeneic HSCT, as for other forms of cellular therapy in solid tumours [146–148], still require further prospective trials, which should be a priority for medical oncology [147–150]. In the absence of new evidence and trials, the new recommendations in 2019 do not change prior indications in solid tumours and are summarised here.

The role of high-dose chemotherapy and autologous HSCT in breast cancer at high risk of recurrence has been assessed by seven randomised trials and a subsequent meta-analysis of individual patient data [151, 152]. As discussed in more detail in the previous report, the overall conclusion from these studies is that autologous HSCT in breast cancer improves progression-free survival but not OS. However, autologous HSCT may still represent a clinical option for

younger patients harbouring HER2-negative tumours and having gross involvement of axillary nodes (adjuvant setting) or highly chemosensitive disease (advanced setting) [153–155].

In germ cell tumours, high-dose therapy and autologous HSCT is a standard of care for patients refractory to platinum-based chemotherapy or with a second or further relapse, excluding primary mediastinal disease, a clinical option as a second line in high-risk patients and generally not recommended as first-line therapy [156–160]. A randomised study comparing conventional dose therapy with high-dose therapy is ongoing ("Tiger study"). Finally, high-dose therapy can be regarded as a potential clinical option in selected patients with Ewing's sarcoma and medulloblastoma [161, 162].

Autoimmune diseases (AD)

AD have been treated with HSCT for over two decades and are currently the fastest growing indication group [21–23]. Both autologous and allogeneic HSCT may be considered patients with severe AD resistant to standard therapies [163–166]. Multidisciplinary guidelines were published by the EBMT in 2012 to cover general principles of patient selection, stem cell collection, graft manipulation, conditioning regimens, supportive care and follow-up [166]. Since then, recent studies have increased the evidence base for autologous HSCT in some indications, including multiple sclerosis [167–171], systemic sclerosis [172–175], Crohn's disease [176–178] and systemic lupus erythematosus [179]. Disease-specific recommendations are increasingly available from the EBMT and other professional societies as the evidence base for autologous HSCT growth [180–183]. Allogeneic HSCT has been predominantly used in the paediatric setting [164], particularly in patients with refractory autoimmune cytopenia and juvenile idiopathic arthritis [184, 185]. It may also be considered on an individual case basis for other rare indications, including monogenic AD, with appropriate specialist expertise. Syngeneic as an alternative to autologous HSCT may be considered with comparable risks and potential greater benefit according to donor-related issues. Specific indications for HSCT for adults with AD are presented in Table 1 and supported in more detail in the clinical guidelines published by the EBMT and other professional societies.

Transplant indications in children and adolescents

Allogeneic HSCT in children and adolescents represent over 20% of all allogeneic HSCT activity, with a particular use in rare and congenital diseases. Transplant complications in these patients associate with the vulnerability of the developing child, including development-related organ dysfunction, delayed hormonal development, growth retardation and a high-risk for malignancies in congenital disorders with chromosomal breakage syndromes. Improvements in high-resolution HLA matching for unrelated donors, conditioning regimens and supportive care for infectious and non-infectious complications have progressively reduced mortality and encouraged the positioning of allogeneic HSCT particularly in non-malignant indications at an earlier stage in the course of the disease with patients in a better performance status rather than as a "last chance for cure." Currently, acute and especially chronic GVHD remain the main complications to tackle and the major limitations for patients without optimal matched donors. New allogeneic HSCT strategies will hopefully consolidate improved outcomes as well with MMAD. The updated 2019 classification of HSCT procedures in children and adolescents is shown in Table 2.

Acute myeloid leukaemia

Childhood AML is a rare and heterogeneous disease, with increasing rates of cure and survival with intensive chemotherapy, in particular for patients with favourable prognostic markers. Thus, allogeneic HSCT is not recommended as front-line therapy in low-risk patients but remains a standard of care for patients in CR1 with high and very high risk with a well-matched donor [186–189]. Alternative donors, in particular haploidentical family members, have also an increasingly relevant role in high- and very-high-risk childhood AML and in patients beyond CR1 [190, 191]. Children who experience AML relapse and reach a second CR are candidates for allogeneic HSCT from the best available donor. Autologous HSCT has been used as consolidation in children with high- and very-high-risk AML in CR1 who lacked a matched allogeneic donor. However, results of paediatric studies on autologous HSCT were conflicting. Therefore, autologous HSCT in this setting is generally not recommended outside prospective trials [192].

Acute lymphoblastic leukaemia

Allogeneic HSCT from matched sibling donors and MUDs is a standard of care for high-risk ALL patients in CR1 and for those in CR2 or later [193–197]. While classical risk factors include molecular markers, chromosomal abnormalities and biological factors including poor prednisone response and resistance to initial chemotherapy [198], MRD has now become the most important prognostic factor to discriminate high and very-high ALL risk

Table 2 Proposed classification of transplant indications for children and adolescents—2019

Disease	Disease status and subtypes	MSD Allo	MUD Allo	MMAD Allo	Auto
Haematological malignancies					
AML	CR1 (low risk)[a]	GNR/II	GNR/II	GNR/III	GNR/II
	CR1 (high and very high risk)[a]	S/II	S/II	CO/II	GNR/II
	CR2	S/II	S/II	S/II	GNR/II
	>CR2	S/II	CO/II	CO/II	GNR/II
ALL	CR1 (low risk)[a]	GNR/II	GNR/II	GNR/III	GNR/II
	CR1 (high risk)[a]	S/II	S/II	CO/II	GNR/II
	CR2	S/II	S/II	CO/II	GNR/II
	>CR2	S/II	S/II	CO/II	GNR/II
CML	First CP, failing second- or third-line TKI	S/II	S/II	CO/II	GNR/III
	Accelerated phase, blast crisis or >first CP	S/II	S/II	CO/II	GNR/III
MDS and JMML		S/II	S/II	CO/III	GNR/III
NHL	CR1 (low risk)	GNR/II	GNR/II	GNR/II	GNR/II
	CR1 (high risk)	CO/II	CO/II	CO/II	CO/II
	CR2	S/II	S/II	CO/II	CO/II
HL	CR1	GNR/II	GNR/II	GNR/II	GNR/II
	First relapse, CR2	CO/II	CO/III	CO/III	S/II
Non-malignant disorders and solid tumours					
Primary ID	Severe combined ID	S/II	S/II	S/II	NA
	Other primary ID	S/II	S/II	CO/II	NA
MPS	MPS-1H Hurler	S/II	S/II	CO/II	NA
	MPS-1H Hurler Scheie (severe)	GNR/III	GNR/III	GNR/III	NA
	MPS-VI Maroteaux-Lamy	CO/II	CO/II	CO/II	NA
Thalassemia and SCD		S/II	CO/II	CO/II	NA
Osteopetrosis		S/II	S/II	S/II	NA
Acquired SAA		S/II	S/II	CO/II	NA
IBMFS		S/II	S/II	CO/II	NA
Germ cell tumours		CO/II	CO/II	CO/II	CO/II
Sarcoma	Ewing's sarcoma (high risk or >CR1)	D/II	D/III	D/III	S/II
	Soft tissue sarcoma (high risk or >CR1)	D/II	D/II	D/III	CO/II
	Osteogenic sarcoma	GNR/III	GNR/III	GNR/III	D/II
Neuroblastoma	High risk or>CR1	CO/II	CO/II	D/III	S/II
Brain tumours		GNR/III	GNR/III	GNR/III	CO/II
Wilms' tumour	>CR1	GNR/III	GNR/III	GNR/III	CO/II
AD	Including monogenic AD	CO/II	CO/II	CO/II	CO/II

AD autoimmune disorders, *ALL* acute lymphoblastic leukaemia, *Allo* allogeneic transplantation, *AML* acute myeloid leukaemia, *Auto* autologous transplantation, *CML* chronic myelogenous leukaemia, *CO* clinical option (can be carried after careful assessment of risks and benefits), *CR1, 2* first, second complete remission, *D* developmental (further trials are needed), *GNR* generally not recommended, *HL* Hodgkin lymphoma, *HSCT* haematopoietic stem cell transplantation, *IBMFS* inborn marrow failure syndromes (Fanconi anaemia, dyskeratosis congenita, Blackfan–Diamond anaemia and others), *ID* immunodeficiency, *JMML* juvenile myelomonocytic leukaemia, *MDS* myelodysplastic syndromes, *MMAD* mismatched alternative donors (cord blood, haploidentical and mismatched unrelated donors), *MPS* mucopolysaccharidosis, *MSD* matched sibling donor, *MUD* well-matched unrelated donor (8/8, 10/10 or 9/10 if mismatched is in DQB1), *S* standard of care (generally indicated in suitable patients), *SAA* severe aplastic anaemia, *SCD* sickle cell disease (high risk). This classification does not cover patients for whom a syngeneic donor is available

[a]Categories are based on number of white blood cells, cytogenetics and molecular markers at diagnosis and time to achieve remission (see text)

groups [199–201]. If a matched sibling or a MUD cannot be identified, MMAD such as CB, MMUD or haploidentical family donors are a clinical option [202]. In contrast to adults, stem cells from PB show no advantage in engraftment or relapse incidence compared to BM and therefore BM is the preferred stem cell source for children [203]. New developments from clinical trials such as the AIEOP-BFM ALL 2017 (ClinicalTrials.gov Identifier: NCT03643276) will provide in the coming years evidence for an innovative integrated approach to identify patients at high risk with an indication for an allogeneic HSCT based on response to treatment, remission status at defined check-points, molecular markers and a combination of MRD status with genetic aberrations and reorient the therapy accordingly.

Chronic myeloid leukaemia

As discussed earlier for adult patients, since the advent of TKIs, allogenic HSCT is not recommended as first-line treatment of CML in children and adolescents either. However, it remains a standard option for patients with treatment failure, recurrence after receiving salvage second-generation TKI treatment and advanced-phase CML [204–206]. Of particular relevance for paediatric patients, the indication for allogeneic HSCT in CML needs careful individual consideration to balance the well-established long-term complications of HSCT with adverse events from prolonged TKI treatment that may include growth failure, hepatic and cardiac complications [207–209]. Stronger evidence from prospective cooperative studies will be needed to address disease evolution after TKI discontinuation and other issues specifically in paediatric patients with CML [205, 210].

MDS and juvenile myelomonocytic leukaemia

Allogeneic HSCT from a sibling donor or a MUD is the treatment of choice for children with primary MDS including juvenile myelomonocytic leukaemia, as well as secondary AML [211–213]. Autologous HSCT is not recommended outside clinical trials.

Lymphoma

Nearly all children and adolescents with Hodgkin and non-HL are cured with multidrug chemotherapy. Few such paediatric patients are eligible for HSCT (Table 2) [214–218]. In particular, patients with residual disease after re-induction therapy of contemporary chemotherapy-protocols, patients with early NHL-relapses or patients with inadequate response or relapse of ALK-positive anaplastic large cell lymphoma. All other approaches should be discussed with the experts of the front-line chemotherapy trials.

Inherited diseases

Primary immunodeficiencies (PID)

Primary immunodeficiencies are genetic disorders characterised by defective or impaired innate or adaptive immunity. Recurrent, persistent or opportunistic infections are the classic hallmarks of primary immunodeficiencies, although immune-dysregulation, auto-immunity and malignancies are increasingly recognised as presenting symptoms and disease manifestations. While severe combined immunodeficiencies (SCID) usually lead to death during infancy or early childhood unless treated appropriately, other immunodeficiencies lead to serious morbidity, decreased quality of life and associate with premature death through childhood or early adulthood. Allogeneic HSCT can cure most cellular immunodeficiencies affecting innate or adaptive immunity. However, the clinical heterogeneity and frequent lack of strict genotype–phenotype correlation in patients with PID underlines the need for careful, multidisciplinary evaluation of individual patients by experienced teams in order to tailor treatment and allogeneic HSCT according to the exact diagnosis and available donors. Detailed recommendations on allogeneic HSCT for each particular PID and other inherited conditions fall beyond the scope of this manuscript and guidelines are regularly reviewed by the EBMT Inborn Errors Working Party (https://www.ebmt.org/working-parties/inborn-errors-working-party-iewp). Beyond the main indication in children and adolescents, allogeneic HSCT is also a clinical option in young adults with PID (see Table 1) [219, 220].

- *Severe combined immunodeficiency*: SCID diagnosis is a paediatric emergency and patients should undergo allogeneic HSCT from a suitable related, unrelated or alternative donor as soon as possible, obtaining survival rates of >90% when carried out shortly after birth [221–223]. Factors such as the type of SCID (B-lymphocyte+ vs B-lymphocyte−), patient age and status at the time of diagnosis, in particular the presence of viral respiratory infections, and the type of donor and degree of HLA histocompatibility determine the need for conditioning regimen, the recovery of B lymphocyte function and overall outcomes after HSCT [224]. Gene therapy may represent a valid alternative to allogeneic HSCT for selected well-characterised genetic subgroups of SCID, such as adenosine deaminase-deficient SCID [225, 226], although the experience in this field remains limited and requires further follow-up.

- *Other primary immunodeficiencies*: Allogeneic HSCT can cure most of the T-lymphocyte immunodeficiencies such as CD40 ligand deficiency [227], Wiskott-Aldrich syndrome [228, 229], phagocyte disorders such as leukocyte adhesion deficiency and chronic granulomatous diseases [230, 231], haemophagocytic syndromes such as familial lymphohistiocytosis and a growing number of other immunodeficiencies. These patients require conditioning. Survival is similar using an HLA-identical family donor or HLA-matched unrelated donor [224]. Patients transplanted at an early age have a better outcome than those transplanted when older. Gene therapy is also a feasible alternative in some patients with other PID, although currently only available in the context of clinical trials [232].

Inherited diseases: metabolic diseases

Most of the metabolic diseases considered for HSCT are lysosomal storage diseases that rely on transfer of enzyme from donor-derived blood cells to the reticuloendothelial system and solid organs. The successful outcome of HSCT can be affected by the lack of engraftment (secondary rejection is comparatively common), the enzyme levels of the donor (lower if they are a sibling carrier of the disease), the degree of sustained donor chimerism and possibly the immune responses against the unknown donor enzyme [233, 234]. In recent years, HSCT outcomes with both MUD and CB donors has gradually improved by adapted transplant strategies including busulfan pharmacokinetic monitoring to improve chimerism and concomitant enzyme levels [235, 236]. In diseases with CNS involvement, amelioration is dependent on the replacement of recipient microglial cells by cells of donor origin. Given the speed of disease progression and the fact that the process to remove abnormally stored debris by donor cells is slow, this delay until disease stabilisation post-HSCT needs to be taken into consideration in decision making towards HSCT (allowing for a donor search, clinical assessment and conditioning). Gene therapy may have a role in selected metabolic disorders, as recently reported in metachromatic leukodystrophy and cerebral adrenoleukodystrophy [237, 238].

Haemoglobinopathies

Allogeneic HSCT from a healthy related sibling donor or a related CB represents the treatment of choice for young patients with severe forms of β-thalassaemia. For patients without an MSD, a transplant from a MUD is a clinical option [239–243]. HSCT from haploidentical related donors is now increasingly performed as a clinical option in experienced centres [244–247]. The outcome of HSCT for thalassaemia has progressively improved with the identification of the Pesaro risk classes and the development of new conditioning regimens and supportive therapies. They should be performed early in life to reduce complications, and iron overload should be assessed before HSCT and intensive chelation therapy performed, as required. The mortality of children with sickle cell disease has reduced significantly with simple measures of conventional therapy such as vaccination, antibiotic treatment, parent education and the use of hydroxyurea starting in infancy. Nevertheless, adult mortality of these patients has only shifted to older ages as conventional therapies do not have an impact on systemic vasculopathy. Therefore, adults continue to succumb to heart, pulmonary, renal failure and stroke and remain often disabled many years prior to these terminal events. For this reason, HSCT from an MSD or from a MUD should be offered [248–250]. Haploidentical HSCT, initially characterised by high rates of graft rejection, is increasingly considered as a clinical option using either post-transplant cyclophosphamide or T cell-depleted strategies [251]. Sickle cell disease is a multiorgan disease with unexpected and disease-specific complications such as neurotoxicity and PRES and experimental approaches should therefore only be performed in controlled clinical trials in highly experienced centres [252]. Lentiviral and crispr/cas9 gene therapy approaches are currently evaluated as potential alternatives to allogeneic HSCT. A recently reported lentiviral-based gene therapy approach for beta-thalassemia has been submitted for market authorisation [253].

Osteopetrosis

Malignant infantile osteopetrosis is a rare inherited (autosomal recessive) type of skeletal dysplasia which manifests in infancy and is characterised by osteoclast deficiency resulting in increased bone density, pancytopenia from medullary obliteration, cranial nerve compression and pathologic fractures. The prognosis is poor with most untreated children not surviving past their first decade. For most genetic forms, allogeneic HSCT from MSD, MUD or MMAD is recommended as an effective therapeutic option for these patients, with resolution of skeletal radiographic features, and with recent improved outcomes using reduced-intensity protocols [254–257].

Acquired SAA and inherited BM failure syndromes

Allogeneic HSCT from an MSD is the standard front-line therapy for children with acquired SAA. In patients without an MSD, a well-matched unrelated HSCT is now also considered a standard front-line therapy in many patients if the donor is readily available, and the search should in any

case be initiated before starting any immunosuppressive therapy [258–262]. For those who fail their first course of immunosuppression, if a MUD is identified, the transplant or a second course of immunosuppression should be given, according to clinical status. Children with Blackfan–Diamond anaemia having an MSD should be transplanted if they do not respond to steroids. If a matched sibling donor is not available, allogeneic HSCT may be performed with a MUD in experienced centres [263]. Children with Fanconi anaemia [138–140], dyskeratosis congenital [141–143] and other inherited BM failure syndromes shall also be transplanted if they have an HLA-identical sibling donor or a MUD (see above). For patients who lack a well-matched donor, HSCT from MMAD should be considered as a clinical option in the context of a clinical protocol.

Solid tumours

Although the published results have not proven yet as an unequivocal benefit for most indications, children and adolescents with solid tumours can undergo autologous HSCT following high-dose chemotherapy as a clinical option or within research protocols, preferably as part of first-line treatment strategies, as described in Table 2. Neuroblastoma (stage 4 beyond the age of 1 year or high-risk factors in lower stages) is still the only indication where the benefit of autologous HSCT has been demonstrated by randomised trials [264, 265]. In general, allogeneic HSCT in children with solid tumours should only be explored within prospective clinical trials in highly experienced centres.

Autoimmune diseases

Autologous and allogeneic HSCT may be considered as a clinical option for children and adolescents with AD [163–166]. Autologous HSCT may be considered for carefully selected subpopulations of patients with juvenile inflammatory arthritis (e.g. polyarticular course or onset, inadequate response and/or intolerance to prednisone or disease-modifying antirheumatic drugs) and other AD, including systemic sclerosis, systemic lupus erythematosus, vasculitis and polymyositis-dermatomyositis. Paediatric multiple sclerosis is a rare indication for autologous HSCT, but long-term responses have been reported [266]. Autologous and allogeneic HSCT have both been performed in severe autoimmune cytopenias, with similar outcomes [184]. Crohn's disease is a potential indication for autologous HSCT, but allogeneic HSCT is appropriate for monogenic forms of inflammatory bowel disease (e.g. interleukin-10 signalling defects, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome, Wiskott–Aldrich syndrome or increasingly X-linked inhibitor of apoptosis deficiency] [182]. Allogeneic HSCT may result in long-term responses in severe juvenile inflammatory arthritis [185]. Overall, given the overlap between autoimmune, auto-inflammatory and primary immunodeficiency diseases in the paediatric age group, there should be appropriate specialist expertise in diagnostics and appraising alternative treatment options in the selection of patients for HSCT. Special consideration should be given to autoimmune diseases with a strong genetic component, for which allogeneic HSCT is appropriate.

The impact of a quality system on the outcome of HSCT

In over two decades since the first EBMT indications manuscript [1], the various editions of this report have incorporated changes in clinical practice coming from scientific and technical advances in the field [2–6]. In this same period, a remarkable development in HSCT has been the establishment of JACIE, an internationally harmonised accreditation system based on agreed quality standards and implemented by teams of voluntary inspectors [267]. Since the first set of standards were approved by the EBMT General Assembly in March 1998, JACIE has promoted high-quality patient and donor care and laboratory performance in HSCT and cellular therapy. Revisions of the standards, in collaboration with the Foundation for the Accreditation of Cellular Therapy, have involved international experts and public consultation and led to standards not only for good practice in HSCT but also for other technologies such as extracorporeal photopheresis and immune cellular therapies. Currently, the standards are in their Seventh edition and have been expanded to incorporate immune effector cell therapies, such as CAR-T cells. JACIE has been recognised by governmental bodies and competent authorities in several EU member states and extends beyond Europe with accredited centres in the Eastern Mediterranean, South Africa and Asia. In the near future, JACIE accreditation is expected to expand further and to become an essential prerequisite in the clinical development and use of novel generation cellular therapies and gene therapies that are reaching the market. JACIE is also working with others within EBMT to provide guidance for patients and for non-specialist clinicians looking after patients with some indications that benefit from HSCT [268].

Importantly, the introduction of a quality management system and other aspects of JACIE accreditation appear to have an impact on survival outcomes and donor safety. Several EBMT studies have correlated JACIE accreditation with improvements in patient survival and reduction in procedural mortality, generally and in specific indications

Table 3 One-year overall survival for the commonest standard-of-care indications for allogeneic and autologous HSCT

Disease	Disease status	MSD Allo	MUD Allo	Auto
Adults				
AML	CR1	74.1% [72.2–76.1]	72.7% [70.7–74.7]	—
	≥CR2	67.9% [62.7–73.1]	70.6% [66.0–75.2]	—
ALL	Philadelphia−, CR1 (high risk)[a]	79.2% [72.9–85.6]	77.3% [69.9–84.7]	—
	Philadelphia+, CR1	79.9% [74.7–85.1]	83.5% [77.8–89.1]	—
MDS	All advanced forms	71.1% [68.4–73.7]	67.1% [64.7–69.5]	—
DLBCL	Chemosensitive relapse, ≥CR2	—	—	79.0% [76.1–82.0]
MCL	CR/PR>1, no prior Auto	—	—	87.8% [80.1–95.4]
FL	Chemosensitive relapse, ≥CR2	—	—	86.0% [80.6–91.4]
HL	Chemosensitive relapse, no prior Auto	—	—	95.4% [92.7–98.0]
MM	First Auto	—	—	94.2% [93.8–94.6]
Acquired SAA		87.9% [84.3–91.6]	76.3% [69.7–82.9]	—
Children and adolescents				
ALL	CR 1	87.7% [82.8–92.5]	82.9% [75.8–90.0]	—
	CR≥2	74.6% [67.7–81.6]	82.1% [76.2–88.0]	—
AML	CR 1	83.7% [78.1–89.3]	79.9% [72.3–87.4]	—
	CR≥2	75.8% [61.6–90.1]	78.5% [68.5–88.6]	—
SCID		93.8% [87.8–99.7]	91.3% [79.8–100]	—
Ewing's sarcoma	High risk or >CR1	—	—	81.0% [73.0–89.1]
Neuroblastoma	High risk	—	—	85.5% [82.4–88.5]
Thalassaemia		94.0% [91.0–96.9]	—	—
Acquired SAA		90.7% [86.3–95.1]	89.4% [83.5–95.4]	—

ALL acute lymphoblastic leukaemia, *Allo* allogeneic transplantation, *AML* acute myeloid leukaemia, *Auto* autologous transplantation, *CR1, 2* first, second complete remission, *DLBCL* diffuse large B cell lymphoma, *FL* follicular lymphoma, *HL* Hodgkin lymphoma, *HSCT* haematopoietic stem cell transplantation, *MCL* mantle cell lymphoma, *MDS* myelodysplastic syndromes, *MM* multiple myeloma, *MSD* matched sibling donor, *MUD* well-matched unrelated donor (8/8, 10/10 or 9/10 if mismatched is in DQB1), *PR* partial response, *SAA* severe aplastic anaemia

[a]Categories are based on number of white blood cells, cytogenetics and molecular markers at diagnosis and time to achieve remission (see text). The analysis includes 37,158 first HSCT reported to EBMT in 2014–2016: 6982 matched-sibling allogeneic, 5853 matched-unrelated allogeneic, and 24,323 autologous; 33918 adults and 3240 paediatric. Overall survival is defined and calculated as per the EBMT Statistical Guidelines [276], and data presented as median [95% confidence interval]

[164, 267, 269–272], as well as in improved donor outcomes [273, 274]. In addition, beyond standards focused on quality of the procedures, JACIE has also recently incorporated standards on patient outcomes with a focus on the quality of the results of the procedures, namely OS (standard B4.7.5) and non-relapse mortality (standard B4.7.6). Such results and patient outcomes following HSCT traditionally come from prospective clinical trials and retrospective registry studies, such as those on which we base our recommendations for the main transplant indications in this manuscript. Most of those studies provide results for particular disease indications, patient characteristics, conditioning regimens and/or stem cell sources, and while informative in such study groups, they are hard to extrapolate to other patient populations. Here we provide an additional set of data from the EBMT Registry with hard outcomes from 37,158 first HSCT in the commonest standard-of-care indications reported to EBMT in 2014–2016, 24,323 autologous and 12,835 allogeneic, 33,918 adults and 3240 paediatric. Tables 3 and 4 include OS at 1 year and non-relapse mortality at day 100 after HSCT, respectively, for such S indications regardless of other patient or transplant factors that are normally considered in traditional prospective and retrospective studies. However, adequate benchmarking that takes into consideration the heterogeneity of the disease, patient and transplant characteristics is significantly more complex than what can be withdrawn from such reference studies or registry data sets. Also, it is questionable for instance whether non-relapse mortality, which is influenced by the occurrence of relapse, can provide interpretable results for a benchmarking strategy unless integrated with an analysis of the latter. The Centre for International Blood and Marrow Transplant Research (www.cibmtr.org) has developed a risk-adapted system for 1-year OS outcome benchmarking, which focuses on allogeneic HSCT outcomes, and several other strategies have been developed and are being implemented in various countries inside and outside Europe. In close

Table 4 Non-relapse mortality at day 100 for the commonest standard-of-care indications for allogeneic and autologous HSCT

Disease	Disease status	MSD Allo	MUD Allo	Auto
Adults				
AML	CR1	4.4% [3.7–5.3]	5.2% [4.3–6.1]	—
	≥CR2	5.1% [3.3–7.6]	6.3% [4.4–8.8]	—
ALL	Philadelphia−, CR1 (high risk)[a]	2.2% [0.8–4.8]	4.2% [1.8–8.0]	—
	Philadelphia+, CR1	5.1% [3.0–8.0]	6.1% [3.4–9.9]	—
MDS	All advanced forms	7.0% [5.7–8.3]	11.5% [10.0–13.1]	—
DLBCL	Chemosensitive relapse, ≥CR2	—	—	5.1% [3.8–6.6]
MCL	CR/PR > 1, no prior Auto	—	—	3.0% [0.8–7.9]
FL	Chemosensitive relapse, ≥CR2	—	—	1.4% [0.4–3.7]
HL	Chemosensitive relapse, no prior Auto	—	—	2.2% [1.0–4.3]
MM	First Auto	—	—	0.9% [0.8–1.1]
Acquired SAA		5.1% [3.2–7.7]	11.9% [7.6–17.2]	—
Children and adolescents				
ALL	CR 1	4.4% [2.3–7.7]	2.1% [0.6–5.5]	—
	CR≥2	5.2% [2.7–8.7]	5.0% [2.6–8.7]	—
AML	CR 1	4.0% [2–7.1]	3.4% [1.3–7.4]	—
	CR≥2	0%	5.4% [1.7–12.2]	—
SCID		4.7% [1.2–11.9]	4.3% [0.3–18.7]	—
Ewing's sarcoma	High risk or >CR1	—	—	0.8% [0.1–3.8]
Neuroblastoma	High risk	—	—	1.7% [1.0–2.8]
Thalassaemia		3.8% [2.0–6.5]	—	—
Acquired SAA		4.4% [2.2–7.8]	4.2% [1.6–8.9]	—

ALL acute lymphoblastic leukaemia, *Allo* allogeneic transplantation, *AML* acute myeloid leukaemia, *Auto* autologous transplantation, *CR1, 2* first, second complete remission, *DLBCL* diffuse large B cell lymphoma, *FL* follicular lymphoma, *HL* Hodgkin lymphoma, *HSCT* haematopoietic stem cell transplantation, *MCL* mantle cell lymphoma, *MDS* myelodysplastic syndromes, *MM* multiple myeloma, *MSD* matched sibling donor, *MUD* well-matched unrelated donor (8/8, 10/10 or 9/10 if mismatched is in DQB1), *PR* partial response, *SAA* severe aplastic anaemia

[a]Categories are based on number of white blood cells, cytogenetics and molecular markers at diagnosis and time to achieve remission (see text). The analysis includes 37,158 first HSCT reported to EBMT in 2014–2016: 6982 matched-sibling allogeneic, 5853 matched-unrelated allogeneic, and 24,323 autologous; 33,918 adults and 3240 paediatric. Non-relapse mortality is defined and calculated as per the EBMT Statistical Guidelines [276], and data presented as median [95% confidence interval]

collaboration with these partners, the EBMT is taking the opportunity of the Registry upgrading to the new MACRO platform (Project 2020; https://www.ebmt.org/ebmt/news/update-benchmarking-bmt-survival-outcomes-work-ebmt-project-2020-clinical-outcomes-group) to develop the statistical methodology for a universally available risk-adapted benchmarking system. Soon this will enable EBMT member centres to benchmark their survival outcomes against national and/or international norms, irrespective of the size of their HSCT community.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest for this manuscript.

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