A compendium of evidence and framework for neuropsychological services in paediatric cancer

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Disclaimer: The information presented in this report is considered to be true and correct at the date of publication.
**Abbreviations**

ALL  Acute Lymphoblastic Leukaemia  
AML  Acute myeloid leukaemia  
Ara-C  Cytarabine  
BASC2  Behavior Assessment System for Children, Version 2  
BMT  Bone marrow transplant  
BRIEF  Behavior Rating Inventory for Executive Functions  
BT  Brain tumour  
CCC  Children’s Cancer Centre  
CNS  Central nervous system  
COG  Children’s Oncology Group  
CSI  Cranial spinal irradiation  
CRT  Cranial radiation therapy  
IQ  Intelligence quotient  
LTFP  Long Term Follow-up Program  
LTFU  Long term follow-up  
MCH  Monash Children’s Hospital  
MD  Multidisciplinary  
MRI  Magnetic resonance imaging  
MTX  Methotrexate  
NHL  Non-Hodgkin’s Lymphoma  
PF  Posterior fossa  
PFS  Posterior Fossa Syndrome  
PICS  Paediatric Integrated Cancer Service  
RCH  The Royal Children’s Hospital  
TBI  Total body irradiation  
WM  Working memory  
VCAP  Victorian Cancer Action Plan

**Definitions**

The terms **neurocognitive**, **neurobehavioural** and **neuropsychological** are used interchangeably in this document. They are defined as, being of, or relating to, the action of the central nervous system and behaviour/cognition.

**Late effects**: Treatment sequelae that occur in the months to years’ post-treatment for childhood cancer.
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Executive summary
Survival rates for childhood cancer patients have reached 80-90% for the most common diagnoses. With a growing population of survivors, much of the focus of treatment protocols has shifted to improving health-related and psychosocial quality of life outcomes. Neurobehavioural late effects are an area of major concern for patients and families, with significant implications for long-term academic, vocational and social success. Unlike some other areas of morbidity, they are potentially amenable to intervention, presenting a unique opportunity to improve outcomes through proactive and targeted interventions.

Objectives
The current project was commissioned by the Paediatric Integrated Cancer Service (PICS) to support The Royal Children’s Hospital (RCH) and Monash Children’s Hospital (MCH) Children’s Cancer Centres (CCC’s) in the documentation of a model of care for the health services. The project consisted of four broad aims;

(i) To review the current literature regarding neurobehavioural late effects in childhood cancer survivors. Specifically, to ascertain the presence of risk indicators that might identify children at high/moderate risk of cognitive or behavioural deficits following treatment.

(ii) To review available international guidelines for neurocognitive assessment and follow-up for childhood cancer patients to inform local services.

(iii) To document findings from local studies regarding neurobehavioural outcomes for the population of children treated through the CCC’s at the RCH and MCH, and to highlight the implications of these findings for assessment and monitoring of this patient group.

(iv) To establish a risk algorithm using international guidelines and local data that could inform workforce requirements for neuropsychology services.

Findings
- Approximately 80-100% of malignant brain tumour patients and 30-50% of leukaemia patients (the 2 most common cancer diagnoses of childhood) will experience long-term neurobehavioural changes that place them at significant disadvantage in regards to their peers in achieving long-term vocational and relationship goals. Local data closely corresponds to the international literature.

- Predicting these outcomes is however hampered by significant individual variability despite the presence of several risk predictors, namely: use of CNS-directed therapies, younger age at diagnosis/treatment, increased time since treatment, female gender, neurological complications, and pre-existing/family history of learning difficulties/developmental disorder.

- In addition, the insidious onset of neurobehavioural late effects makes them difficult to identify at an early stage when interventions are likely to be most effective. Ongoing monitoring is therefore required to examine patterns of change in performance and to identify the onset of difficulties before they affect everyday functioning. This requires formal neuropsychological evaluation for those children at highest risk of late effects, and screening assessments for children at moderate risk.
The Children’s Oncology Group (COG) guidelines for long-term follow up of childhood cancer patients provide clear directives for service development that should be incorporated into local programs.

**Recommendations for service improvement**

A new framework that meets the standards suggested by international consorts and incorporates findings from local population studies is presented. Research and quality review of the service should be in-built to the program to allow for ongoing evaluation of local needs and to inform the development of customised intervention programs. The success of this approach lies in developing joint positions for staff in both clinical and research programs. This will ensure the successful implementation of studies across acute and Long Term Follow-up Program (LFTP) services, and to the translation of research findings into quality improvements in the clinical service.
Introduction

1. Background information

1.1. Childhood cancer

Paediatric cancer is the second most common cause of mortality in Australian children [1]. Approximately 1 in 600 children less than 15 years of age will develop the disease in Australia, with between 150 and 180 new diagnoses in Victoria each year [2]. The most common diagnoses are leukaemia and central nervous system (CNS) tumours, which together account for over 50% of all childhood cancers. Other tumour types include lymphoma, Wilms tumour, neuroblastoma, and bone tumours [2].

1.2. Improved survival rates

In the 1960s, less than 30% of children survived a malignant cancer diagnosis [3]. With advancements in treatment protocols, up to 80-90% of children treated with modern therapies are expected to achieve complete remission and live free of disease well into adulthood [4].

Gains in treatment efficacy have been achieved predominantly through the introduction of multimodal therapies and intensification of treatment regimes, but not without a significant increase in morbidity. Surgery, radiotherapy and chemotherapy remain the mainstay of paediatric cancer treatments, however these techniques are generally nonspecific to cancerous cells, leaving exposed healthy tissues vulnerable to collateral damage. With a growing population of paediatric cancer survivors, the focus of the paediatric oncology community has shifted to long-term quality of life outcomes. The importance of reduced morbidity is highlighted by the use of neurobehavioural outcomes as a measurement of success in current international treatment trials.

1.3. Late effects of therapy

Paediatric cancer survivors face ongoing challenges to their health and wellbeing that can be directly attributed to cancer treatment. Delayed therapy-related sequelae are termed ‘late effects’ in the cancer literature as they develop and become clinically apparent in the months to years following treatment. Late effects are well documented in the survivorship population [5-8] and are often chronic and progressive in nature [5, 9]. It is thought that approximately 65-75% of childhood cancer survivors experience at least one late effect of treatment [10, 11], with 30-40% suffering from sequelae that are severe or life threatening [11, 12]. Late effects of paediatric cancer therapy include cardiopulmonary disease [10, 13, 14], growth impairment [13, 14], endocrinopathies and metabolic disorders [8, 13], musculoskeletal abnormalities including osteoporosis and pathological fractures [13, 14], secondary malignancies [13], renal impairment [13], gastrointestinal dysfunction [5, 13], decreased fertility [15], and neuropsychological deficits [6, 7, 10, 13]. At the most extreme end, the incidence of premature death consequential to late effects is significantly elevated beyond 30 years after diagnosis [7].
2. Neurocognitive late effects

2.1. Established neurocognitive outcomes

Neurocognitive late effects broadly describe the cognitive and behavioural treatment sequelae experienced by a significant number of childhood cancer survivors. The term is most commonly used to refer to deficits in thinking, learning, and memory skills that emerge following treatment [16]. Given the importance of these skills to academic progress, vocational success, and quality of life outcomes, it is not surprising that neurocognitive late effects represent one of the most prominent concerns for families and patients post-cancer treatment [11]. This is enhanced by the unpredictable nature and insidious onset of deficits post-treatment, with changes in ability often not evident until months or years following treatment completion [12, 15, 17, 18].

Approximately 50-60% of all children treated for cancer are at risk of experiencing some form of neurocognitive dysfunction, with rates approaching 100% for children treated for a malignant brain tumour [10, 19]. Neurocognitive dysfunction in CNS tumour and leukaemia survivor populations has been thoroughly documented in the literature over the past 20 years [20, 21], and profiles of neurocognitive morbidity have been established [22]. The high risk status of these groups is attributed to the use of intensive neurotoxic treatments that are directly administered to the central nervous system [22]. Survivors of other cancer types, including lymphoma and osteosarcoma, are also at elevated risk of neurocognitive impairment, although to a lesser extent [21, 23].

2.1.1. Primary neurocognitive outcomes

Core neurocognitive skills affected by CNS-directed cancer therapy are those that are executed within the cerebral cortex, or neural white matter of the brain [24]. Cognitive domains most commonly affected include attention [25-28], working memory [27-29], information processing speed [25, 27, 28, 30], executive function [27, 28, 31], and visuomotor [27, 28, 30] and visuospatial functioning [27, 28]. Profiles of neurocognitive impairment are not uniformly distributed across all childhood cancer survivors. Risk factors for poorer neurocognitive outcome have been clearly elucidated and include CNS-direct therapy, younger age at treatment, and female gender [17]. Factors contributing to neurocognitive morbidity will be discussed in more detail subsequently.

2.1.2. Neurocognitive outcomes in survivors of CNS tumours

For children diagnosed with a brain tumour, the location of the lesion infers a direct insult on developing neural tissue. Aggressive multimodal therapy comprising neurosurgery, cranial irradiation, and chemotherapy may be utilised during treatment. Cranial radiation therapy (CRT) is the mainstay of treatment for CNS tumours and has consistently been associated with late arising neurocognitive impairment [32, 33]. It is estimated that between 40-100% of children diagnosed with a brain tumour will experience some degree of neurocognitive morbidity following such intensive therapy [16].

Ellenberg et al. (2009) found that survivors of CNS malignancies were significantly more likely to report neurocognitive impairment than their siblings or survivors of other cancers. Specifically,
survivors of CNS tumours reported problems with memory, emotional regulation, organisation, and task efficiency (processing speed, self-initiation, and multitasking) at a greater rate than siblings or survivors of non-CNS malignancies. Task efficiency and memory were highly correlated with each other, suggesting that core domains of cognition are interrelated to some degree [34].

### 2.1.3. Neurocognitive outcomes in survivors of leukaemia

Historically, cranial irradiation was used as a measure of CNS prophylaxis in all children treated for leukaemia. However, detrimental neurocognitive outcome following cranio-spinal irradiation (CSI) in survivors of leukaemia was consistently reported [35, 36]. Hence, CRT was replaced with intrathecal and systemic chemotherapy in low- and standard-risk leukaemia treatment protocols [22]. Despite early literature surrounding the presence of chemotherapy-induced neurocognitive sequelae being inconsistent [37-39], it is now widely accepted that certain chemotherapeutic agents (i.e. methotrexate, cytarabine), and corticosteroids produce neurocognitive effects similar to those arising from CRT, although deficits are more subtle in nature [25, 40, 41]. Kadan-Lottick and colleagues (2010) found that non-CNS cancer survivors were likely to complain of neurocognitive difficulties at approximately double the rate of their siblings, particularly in the areas of memory, emotional regulation, and task efficiency [23].

While assessing behavioural and educational difficulties in survivors of leukaemia, Buizer et al. (2006) found that poorer neurocognitive functioning in the area of attention was specifically associated with significantly more problems at school. The researchers concluded that dysfunction in core cognitive domains was not merely subclinical, but may have strong ramifications for daily life [30]. Furthermore, Wolfe et al. (2012) contended that dysfunction in cognitive areas of working memory, information processing speed, and executive function can detrimentally impact educational attainment and adaptive functioning [42].

### 2.1.4. Secondary functional outcomes

Neurocognitive morbidity in core domains of cognition may have widespread consequences on secondary outcome measures such as generalised intelligence, academic achievement, and occupational success. This may subsequently have a negative impact on quality of life. Declines in generalised measures of intelligence (i.e. lowered intelligence quotient, IQ) following treatment for paediatric cancer have been well established [43]. Palmer et al. (2003) examined intellectual function among 50 medulloblastoma patients treated with 35-40 gray CSI with or without chemotherapy over a period of 7-years post-diagnosis. Full scale IQ was found to decline at a rate of 2.05 points per year following diagnosis [44], which is similar to previous estimations of decline ranging from 2.55 to 4.30 points [45-47]. Palmer and colleagues (2003) also found that patients reporting higher IQ at baseline showed a steeper decline in intellectual function over time [44].

Butler et al. (2005) proposed that learning difficulties and academic failure arise as a consequence of damage to core cognitive processes (i.e. slowed information processing, decreased attentional capacity, and poorer memory) [17]. Declines in reading, spelling, and mathematics have been repeatedly demonstrated in children who received CNS-directed therapy [28, 48]. Long-term
survivors had significantly more school absences and were more likely to repeat a grade [48, 49]. Raymond-Speden et al. (2000) found that patients with leukaemia treated prophylactically with CRT and/or intrathecal chemotherapy performed significantly worse in measures of general intelligence and academic functioning (reading, spelling, and arithmetic) when compared to a chronic asthma control group and healthy children. As the chronic asthma control group had similar rates of school absence, these results indicated that the neurocognitive deficits observed were not exclusively the result of school absenteeism, but more likely due to treatment factors [50].

Survivors of all major types of childhood malignancy are more likely to utilise special education services throughout schooling than their siblings or the general population. Enrolment rates ranged from 23 to 32% in childhood cancer survivors compared to less than 15% in healthy children [51-53]. Mitby et al. (2003) found that childhood cancer survivors were less likely to finish secondary schooling unless they were enrolled in a special education program. This was noted for survivors of CNS tumours, leukaemia, and non-Hodgkins lymphoma in particular [53]. In fact, survivors that are placed in special education services achieve comparable secondary school graduation rates and have similar aspirations for tertiary education as healthy children [49, 51]. Unfortunately, not all survivors that may benefit from special education programs necessarily meet functional criteria for enrolment in these services. This may result in poorer school performance overall [30].

Despite consistent findings of academic difficulties in long-term paediatric cancer survivors, not all children seem to be at equal risk for educational failure. Certain subgroups of survivors reliably demonstrate weaker school performance [51, 53]. Survivors at higher risk of academic impairment and requiring special education services include those treated for a brain tumour or leukaemia (i.e. those treated with CNS-directed therapy), children diagnosed at a younger age, and females [17, 54].

Additionally, Kirchhoff et al. (2011) found that adult survivors of childhood cancer were more likely to be employed in lower-skilled work than their siblings. Lower-skilled occupations are frequently associated with reduced job stability, greater exposure to workplace hazards, and increased risk of morbidity and mortality. Furthermore, lifetime earning capacity of less skilled workers is lower [55]. Mulhern and colleagues (2004) and Edelstein et al. (2011) reported significantly higher unemployment rates in survivors of brain tumours than within the general population [43, 56], whereas survivors of non-CNS tumours demonstrated similar occupational outcomes to their peers [49].

2.2. Risk factors for neurocognitive morbidity

There is overwhelming evidence demonstrating the detrimental effects of paediatric cancer treatments on long-term neurocognitive function. It is now thought that at least 50% of childhood cancer survivors who received CNS-directed therapy will ultimately develop some degree of neurocognitive morbidity [19]. It is not possible to accurately predict which children will go on to suffer neurocognitive impairment as a result of paediatric cancer treatments, but several risk factors have been identified.
2.2.1. Disease and treatment related factors

Diagnosis of a paediatric brain tumour or malignancy requiring CNS-directed therapy is an important risk factor for poorer neurocognitive outcome [22]. Children diagnosed with CNS tumours experience the greatest rates of neurocognitive morbidity, with up to 100% of survivors affected [16, 22]. Perioperative complications associated with neurosurgery confer increased risk of neurocognitive dysfunction. Specifically, hydrocephalus requiring a ventriculoperitoneal shunt [22, 57], post-operative seizures [22], neurological deficits including hearing and visual loss [22, 57], multiple surgeries [57], and bacterial CNS infections [57]. Tumours located supratentorially in the cerebral hemispheres are related to lower neurocognitive functioning both at baseline (pre-treatment) assessment and during long-term follow up [57, 58]. Papzoglou et al. (2008) established that the location of brain tumours is associated with different profiles of neurocognitive outcome. Cerebellar tumours were predictive of attentional dysfunction, whereas third ventricular tumours were associated with deficits in memory function [59].

Cancer treatment, particularly cranial irradiation (photon), has consistently been reported as a major risk factor for the development of neurocognitive impairment [27, 57], with higher intensities of radiation correlated with poorer outcomes [11, 22]. Despite the introduction of newer techniques of radiation delivery (i.e. conformal beam radiation and intensity modulated proton therapy that shape radiation beams to avoid healthy brain tissue), research continues to show a significant risk for cognitive and behavioural sequelae for children on these modern protocols [60]. In addition, neurocognitive morbidity has more recently been associated with CNS-directed chemotherapy in leukaemia survivor populations, especially when delivered as part of an intensive treatment regimen [61]. Chemotherapeutic agents that have been identified as contributing to neurocognitive impairment include methotrexate, cytarabine, and corticosteroids such as dexamethasone and prednisolone [13, 22].

Time since treatment is an important risk factor when assessing neurocognitive status [22]. In their study of intellectual function in medulloblastoma survivors, Palmer et al. (2003) noted that progressive declines in IQ had not reached a plateau at 7-years post-diagnosis. As a result, the researchers strongly emphasised the importance of continuing long term follow-up for medulloblastoma patients, as declines in neurocognitive performance may continue well into adolescence and adulthood [44]. Additionally, because toxic CNS-directed therapies appear to target developing neural tissue, the main impact observed is on cognitive skills that are yet to emerge [62]. Thus, declining school performance is typically associated with a reduced rate of skill development over time, rather than being correlated with a loss of preexisting learned information [7].

2.2.2. Patient related factors

Young age at diagnosis and during treatment is a strong risk factor for poor neurocognitive outcome [57, 63, 64]. Mulhern et al. (2005) identified young age as the most prominent risk factor for neurocognitive impairment in survivors of medulloblastoma previously treated with dose-reduced CSI [65]. Andersen (2003) suggested that the prepubertal brain is at increased risk of damage due to its incomplete development. They state that maturational changes in the cortex occur over a lengthy
timeframe, from birth until late adolescence, and that younger, immature white matter is less resilient, and more likely to experience permanent damage as a result of hypoxia or drug exposure [66]. Reddick and colleagues (2006) supported this idea by stating that newly synthesised myelin has a lower stability, making it more susceptible to the neurotoxic effects of treatment [64].

Female gender is frequently associated with lower neurocognitive performance [61, 63, 67, 68]. Buizer et al. (2005) suggested that females may be more vulnerable to the detrimental neurocognitive effects of treatment due to gender differences in brain maturation. These researchers proposed that the increase in white matter during early childhood is smaller in girls than boys, hence leaving females more susceptible to neurotoxic therapies [61].

Research in children with traumatic brain injuries demonstrated reciprocal relationships between family burden, parental distress, and neurocognitive morbidity. Based on these findings, Cant Peterson et al. (2006) suggested that bidirectional relationships may exist between family functioning and neurocognitive outcomes in childhood cancer survivors. The researchers proposed a model of neurodevelopmental late effects and family functioning, which contended that neurocognitive performance and academic reintegration are interdependent with parental understanding of late effects, perceived family burden, family conflict, and parental psychological adjustment [62]. Caregiver stress has been documented in parents of paediatric cancer survivors with neurocognitive difficulties [69]. However, research focused on the interrelationship between neurocognitive late effects and family functioning has not yet been conducted.

Children born with heritable conditions such as Down syndrome, neurofibromatosis type 1, and tuberous sclerosis are at greater risk of developing CNS and non-CNS paediatric malignancies. These children often have marked neurocognitive impairment prior to diagnosis with cancer. As a result, children with genetic conditions are often excluded from research investigating neurocognitive morbidity following cancer treatment, and hence little is known about how cancer therapy affects children with preexisting neurocognitive dysfunction [1].

2.3. Pathophysiology of neurocognitive morbidity

Neural white matter has been identified as the substrate most vulnerable to damage during treatment for childhood cancer. White matter is comprised of axonal bodies that are encased in a layer of fatty tissue called myelin. The myelination process allows for increased speed of neural information transmission between neurons which is essential for effective communication [24]. All three modalities utilised to treat various types of paediatric malignancy have been associated with neurotoxicity and white matter damage.

Surgical resection of brain tumours is critical for effective treatment, however physical disruption of delicate neural tissue may result in neurocognitive morbidity. Although perioperative complications are generally acute in nature [70], it has been suggested that these factors can cause a general compromise of neural integrity that impacts long-term neurocognitive function, resulting in slowed information processing [71].
It is thought that the detrimental late effects of cranial irradiation can be attributed to acute changes in vasculature that lead to decreased oxygenation of neural tissue and irreversible injury. Permanent injuries to the CNS observed following CRT include degeneration of myelin (leukoencephalopathy), calcification, microvascular pathology, tissue necrosis, and cerebral oedema [72].

A wide range of chemotherapeutic agents are applied in the treatment of paediatric cancer. Methotrexate, cytarabine, and dexamethasone have been associated with late neurocognitive morbidity, however the pathological mechanisms underlying drug-induced neurotoxicity have not been fully elucidated. Methotrexate, the most extensively researched chemotherapeutic agent, appears to cause permanent leukoencephalopathy within the brain. Leukoencephalopathy may result from direct toxic effects of methotrexate on myelin, or secondary to immunologic reactions, oxidative stress, neurotransmitter abnormalities, and microvascular injury [70]. Buizer and colleagues (2005) proposed that methotrexate-induced changes in folate metabolism may cause these alterations in brain structure and function [61].

Conventional magnetic resonance imaging was initially used to describe changes in normal appearing white matter volumes of childhood cancer survivors. Reddick and colleagues (2000) established that the volume of normal appearing white matter was decreased in survivors of medulloblastoma [73]. Mulhern et al. (2001) further correlated decreased normal appearing white matter volume with worse neurocognitive performance in a small cohort of medulloblastoma survivors [74]. Similar results are described in leukaemia survivor populations [75]. In addition, Leung and colleagues (2004) demonstrated decreased myelin integrity and density (known as fractional anisotropy) following cranial irradiation in medulloblastoma survivors by using a new imaging technique. The researchers thus suggested that diffusion tensor magnetic resonance imaging could be used to detect and measure neurotoxicity following brain tumour therapy [76]. Schuitema et al. (2013) showed that decreased fractional anisotropy was associated with neurocognitive morbidity in leukaemia survivors [77], a finding that supports previous studies conducted in this area across a range of haematological malignancy and brain tumour survivors [78, 79].

3. Neurocognitive interventions

Research aimed at improving neurocognitive dysfunction in childhood cancer survivors is in its infancy. Methods utilised generally target deficits in attentional ability and/or working memory, as these skills in particular are considered critical for global intellectual function and academic success [80]. Two emerging methods for amelioration of deficits are the pharmacological approach and cognitive remediation.

3.1. Pharmacotherapy

Significant interest has been shown in the role of methylphenidate hydrochloride (MPH), a piperidine derivative that increases dopamine levels in the CNS, in remediation of attentional deficits. Although more commonly used in children with attention deficit hyperactive disorder, MPH
has had success in childhood cancer survivor populations [80-82]. In a recent study, Conklin et al. (2010) documented significant improvements in attentional capacity and behaviour of survivors of leukaemia and brain tumours over a 12-month trial period of MPH [83]. However, there are limitations of pharmacological therapy. Stimulant medications are typically short acting, only efficacious while prescribed, do not result in remediation of deficits, and can be associated with unwanted side effects [84]. Despite this, Nazemi and Butler (2011) recognised the viability of the pharmacological approach and strongly emphasised the need for continuing research into the role of pharmacotherapy in neurocognitive rehabilitation [85].

3.2. Cognitive rehabilitation

Butler and Copeland (2002) proposed a cognitive remediation program for rehabilitation of attentional deficits in childhood cancer survivors. The clinic-based therapeutic approach employed a tripartite model, utilising strategies from traumatic brain injury rehabilitation, educational psychology, and clinical psychology. The program comprised adaptive drill-like exercises combined with compensatory learning strategies such as organisation and behavioural self-monitoring, and was effective at significantly improving attentional skills [86]. Despite being efficacious, clinic-based remediation programs may create additional burden on families. As a result of such criticism, Hardy et al. (2013) devised home-based computerised cognitive rehabilitation program. In their pilot study of the program, the researchers demonstrated good feasibility, acceptability, and significant improvements in visual working memory of survivors of leukaemia and brain tumours [87]. The current literature regarding neurocognitive intervention is promising, showing numerous types of methods with varying efficacy. Despite different methods, it is clear that neurocognitive intervention can be successful in the cognitive and academic remediation of paediatric cancer survivors if applied early [85, 88].

4. Guidelines and screening recommendations for long term follow-up

Despite the identification of several risk factors for neurocognitive late effects, there exists significant individual variability in long-term outcomes that precludes the implementation of a well-defined risk algorithm to predict vulnerability of newly diagnosed patients. As a result of this uncertainty there exists little in the way of published guidelines to provide clear directives on the neuropsychological requirements of children during, or post, cancer treatment.

4.1. St Jude long-term follow-up (LTFU) recommendations

St Jude Children’s Research Hospital, Memphis, a centre of excellence in paediatric oncology care, has published recommendations for risk-based medical follow-up but no specific outline for monitoring of neurobehavioural outcomes. The guidelines hold that the late sequelae of therapy for childhood cancer can be anticipated based on therapeutic exposures, but the magnitude of risk and the manifestations in an individual patient are influenced by numerous factors.
Table 1: St Jude - factors that should be considered in the risk assessment for a given late effect

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Treatment</th>
<th>Host</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Tumour location.</td>
<td>- Radiation therapy: Total dose, fraction size, organ or tissue volume, type of machine energy.</td>
<td>- Gender.</td>
</tr>
<tr>
<td>- Direct tissue effects.</td>
<td>- Chemotherapy: Agent type, dose-intensity, cumulative dose, schedule.</td>
<td>- Genetic predisposition.</td>
</tr>
<tr>
<td>- Tumour-induced organ dysfunction.</td>
<td>- Surgery: Technique, site.</td>
<td>- Premorbid health state.</td>
</tr>
<tr>
<td>- Mechanical effects.</td>
<td>- Hematopoietic cell transplantation.</td>
<td>- Developmental status.</td>
</tr>
<tr>
<td></td>
<td>- Use of combined modality therapy.</td>
<td>- Age at diagnosis.</td>
</tr>
<tr>
<td></td>
<td>- Blood product transfusion.</td>
<td>- Time from diagnosis/therapy.</td>
</tr>
<tr>
<td></td>
<td>- Management of chronic graft-versus-host disease.</td>
<td>- Inherent tissue sensitivities and capacity for normal tissue repair.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Hormonal milieu.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Function of organs not affected by cancer treatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Socioeconomic status.</td>
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<tr>
<td></td>
<td></td>
<td>- Health habits.</td>
</tr>
</tbody>
</table>

The St Jude manifest states, “measurement of functional capacity is central to developing therapeutic strategies to improve quality of life”. Whilst the need for LTFU is seen as essential, the general nature of the St Jude guidelines, and absence of high-risk and low-risk identifiers make it difficult to develop a program to match the level of support required for individual childhood cancer patients, and specifically in regards to neurocognitive outcomes.

4.2. Children’s Oncology Group (COG) LFTU guidelines

The COG consortium has a Behavioural Science Committee made up of a number of prominent psychologists and neuropsychologists practicing in the paediatric oncology field. They contribute to the LTFU guidelines that outline a structured approach to determining risk of neurocognitive late effects, and provide specific recommendations for assessment, monitoring and liaison. In the article published by Nathan et. al. in 2007 to accompany the guidelines, children treated for a brain tumour (BT), acute lymphoblastic leukaemia (ALL), stem cell transplantation, acute myeloid leukaemia (AML), non-Hodgkin lymphoma, and those with tumours of the head and neck (who have undergone radiation therapy) are identified as at risk [19].

The most recent guidelines were published in October 2013 (www.survivorshipguidelines.org).

Risk is defined by treatment type with three agents identified as placing patients at significant risk of neurocognitive late effects; radiation, methotrexate (MTX) and cytarabine (ara-C). Risk is dependent on delivery method as specified:

- Radiation: cranial, ear/infratemporal, and total body irradiation (TBI).
- MTX: Intrathecal, IO (ommaya reservoir) and high-dose intraventricular (defined as any single dose ≥ 1000mg/m²).
- Cytarabine: high-dose intraventricular (defined as any single dose ≥ 1000mg/m²).

Neuropsychological monitoring is also indicated for neurosurgery when it occurs in combination with one of the 3 agents listed above.
For each agent several host, treatment, health behaviours and medical conditions are identified as placing children at risk.

**Table 2: Radiation**

<table>
<thead>
<tr>
<th>Host</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| - Younger age at treatment.  
- Primary CNS tumor.  
- CNS leukemia/lymphoma.  
- Relapsed leukemia/lymphoma.  
- Treated with CNS-directed therapy.  
- Head/neck tumors with brain in radiation field. | - Radiation in combination with:  
Corticosteroids  
Methotrexate (IT, IO, high-dose IV)  
Cytarabine (high-dose IV).  
- Higher radiation dose.  
- Larger radiation field.  
- Greater cortical volumes.  
- Cranial radiation in combination with TBI.  
- Longer elapsed time since therapy. |

**Table 3: MTX**

<table>
<thead>
<tr>
<th>Host</th>
<th>Treatment</th>
<th>Health behaviours</th>
</tr>
</thead>
</table>
| - Younger age at treatment.  
- CNS leukemia/lymphoma.  
- Relapsed leukemia/lymphoma.  
- Treated with CNS-directed therapy.  
- Female sex. | - In combination with:  
Corticosteroids  
TBI  
Cranial radiation  
Cytarabine (high-dose IV).  
- Longer elapsed time since therapy.  
- Hyperthyroidism. | - Inadequate intake of calcium and vitamin D.  
- Lack of weight bearing exercise.  
- Smoking.  
- Alcohol use.  
- Carbonated beverages. |

**Table 4: Cytarabine**

<table>
<thead>
<tr>
<th>Host</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| - Younger age at treatment.  
- CNS leukemia/lymphoma.  
- Relapsed leukemia/lymphoma.  
- Treated with CNS-directed therapy. | - In combination with:  
Corticosteroids  
TBI  
Cranial radiation  
Methotrexate (IT, IO, high-dose IV).  
Cytarabine (high-dose IV).  
- Longer elapsed time since therapy. |

**Table 5: Neurosurgery**

<table>
<thead>
<tr>
<th>Host</th>
<th>Treatment</th>
<th>Medical conditions</th>
</tr>
</thead>
</table>
| - Younger age at treatment.  
- Primary CNS tumor. | - In combination with:  
TBI  
Cranial radiation  
Methotrexate (IT, IO, high-dose IV)  
Cytarabine (high-dose IV).  
- Longer elapsed time since therapy.  
- Extent and location of resection. | - Hydrocephalus/history of shunt placement |
The guidelines also provide a ‘very high-risk’ category for each agent. The factors are similar for all forms of treatment and clearly place children aged less than 3 years at diagnosis/treatment, and those with pre-existing learning difficulties (or family history) at the peak of the vulnerability pyramid.

**Table 6: ‘Very high-risk’ category for each agent**

<table>
<thead>
<tr>
<th>Host</th>
<th>Radiation</th>
<th>MTX</th>
<th>Cytarabine</th>
<th>Neurosurgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Age &lt; 3 years old at time of treatment.</td>
<td>- Age &lt; 3 years old at time of treatment.</td>
<td>- Age &lt; 3 years old at time of treatment.</td>
<td>- Age &lt; 3 years old at time of treatment.</td>
<td></td>
</tr>
<tr>
<td>- Female sex.</td>
<td>- Premorbid or family history of learning or attention problems.</td>
<td>- Female sex.</td>
<td>- Premorbid or family history of learning or attention problems.</td>
<td></td>
</tr>
<tr>
<td>- Temporal lobe field.</td>
<td></td>
<td>- Premorbid or family history of learning or attention problems.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Premorbid or family history of learning or attention problems.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Radiation</th>
<th>MTX</th>
<th>Cytarabine</th>
<th>Neurosurgery</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Medical conditions</th>
<th>Radiation</th>
<th>MTX</th>
<th>Cytarabine</th>
<th>Neurosurgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>- Posterior fossa syndrome.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- CNS infection.</td>
<td></td>
</tr>
</tbody>
</table>

Areas of deficit are listed as:
- Executive function (planning and organisation)
- Sustained attention
- Memory (particularly visual, sequencing, temporal memory)
- Processing speed
- Visual-motor integration
- Learning deficits in math and reading (particularly reading comprehension)
- Diminished IQ
- Behavioural change.

On this basis formal neuropsychological evaluation is recommended to include tests of processing speed, computer-based attention, visual motor integration, memory, comprehension of verbal instructions, verbal fluency, executive function and planning.

Deficits are described as more global (i.e. decline in IQ) for brain tumour survivors, and more specific to information processing domains (e.g. learning disability) for survivors of leukaemia and lymphoma. It is noted that new deficits may emerge over time, thus supporting the role of repeat assessment. Initially referral for formal neuropsychological evaluation for children at risk of neurocognitive late effects is recommended at entry into LTFU regardless of whether there is evidence of CNS injury. Review should be determined periodically as clinically indicated for patients with evidence of impaired educational or vocational progress and in consideration of the anticipated...
trajectory of the emergence of late effects and the child’s specific medical and developmental risk factors.

For those children with neurocognitive deficits on formal assessment, referral to school liaison in the community or cancer centre (psychologist, social worker, school counselor) is recommended to facilitate acquisition of educational resources, and/or social skills training. Furthermore, use of psychotropic medication (e.g., stimulants) or evidence-based rehabilitation training is suggested. For children with significant impairment, referral should occur to community services for vocational rehabilitation or for services for developmentally disabled children.

The COG guidelines establish a service capability framework for LTFU, however the Behavioural Science Committee is clearly aware of the limitations faced by many services regarding the availability of neuropsychological resources. In an attempt to improve the collection of neurocognitive data for their international studies the group developed a modified screening assessment (ALTE07C1) that has replaced all prior neuropsychological batteries in their outcome studies. Embry and colleagues published this information in 2012 in support of promoting repeat neurocognitive assessment for children undergoing CNS-directed therapies [89]. They identify serial assessment as highly desirable to assist with optimal school reintegration, future academic and occupational success for the survivor as an individual, and additionally for research purposes, to characterise the onset and trajectory of neurocognitive morbidity.

In their manuscript Children’s Oncology Group’s 2013 Blueprint for Research: Behavioral Science the group articulated the importance of monitoring neurobehavioural abilities from baseline through to survivorship to inform the success of treatment protocols and lead to early identification and intervention for at-risk children [89]. In addition to the success of the use of an abbreviated battery, the group promote embracing novel technologies such as the computerised battery, Cogstate, which can be administered by all staff. The use of brief neurocognitive screening assessments has also been supported by Krull and colleagues from St Jude Children’s Research Hospital [88]. These researchers published a 30-minute battery that could be used as a reliable method to identify cancer survivors in need of further follow-up whilst not placing unachievable demands on limited neuropsychological resources.
Victorian data on neurocognitive late effects and feasibility of assessment practices

5. A local perspective on neurobehavioural outcomes and needs of our survivor population (research from the RCH CCC psycho-oncology group)

Quality of life and neurobehavioural outcomes were identified as key targets in the RCH CCC strategic planning in 2003-2005. This resulted in a number of quality and service model projects including national and international benchmarking to identify best practice service models and clinical research priorities.

5.1. Establishment of the Neuropsychology Service Model in 2006

In 2006, a group of clinicians from the RCH traveled to North America to visit 5 key providers of paediatric oncology services (Dana Faber Cancer Institute Boston, Children's Hospital of Philadelphia, Children's National Medical Centre Washington, St Jude Children’s Research Hospital Memphis and Texas Children’s Hospital Houston). Their role was to determine the feasibility of an RCH CCC clinical and research psycho-oncology program to assist children with neurocognitive and associated psychosocial late effects secondary to cancer treatment. The major findings and conclusions from this study tour highlighted the need for:

- Local research to map the outcomes/impacts of survivorship issues
- Preclinical research to examine the contribution of host factors to CRT and MTX toxicity
- An established team to develop the radiological imaging potential of the CCC to contribute research on brain changes and the behavioural correlates of this
- Routine screening for children with a brain tumour and other high risk populations, beginning in the acute phases of recovery and continuing (as part of a long term effects clinic) until transition into adult services
- A referral pathway for appropriate clinical services
- An integrated clinical research program that informs clinical practice.

A Research Coordinator position was established with philanthropic funds to scope and facilitate the implementation of key projects and promote integration with specialist clinical services.

5.2. High-risk patients and the St Jude medulloblastoma studies

The population of patients treated for a malignant brain tumour has always been the key focus of Neuropsychology services for the RCH and MCH paediatric cancer services. The RCH CCC has participated in several iterations of the St Jude protocol for medulloblastoma treatment, contributing serial neuropsychological data for a substantial number of local patients both on- and off-treatment. The most recently published outcomes for the St Jude protocol SJMB03 support the high needs of these patients in terms of monitoring of cognitive skills and remediation. In particular this data revealed a significant decline in speed of information processing, particularly for children diagnosed at a young age [90]. Furthermore, significant declines in working memory abilities and
significant increases in parent report of working memory problems on the Behavior Rating Inventory of Executive Function (BRIEF) were found. This was particularly the case for children diagnosed with posterior fossa syndrome (PFS). It has long been known that children experiencing PFS post-surgery for a cerebellar tumour take significantly longer to recover, and the SJMB03 findings confirmed that not only is recovery prolonged, but neurocognitive risk is much higher in this group, with deficits in multiple cognitive (processing speed, working memory, attention executive processes and cognitive efficiency) and academic domains (spelling, reading and math) evident as early as 12 months following diagnosis. These findings confirm the role of cranial radiation in the pathogenesis of cognitive late effects, and support the current model of care which places children undergoing CRT at the top of the risk pyramid and highlights the need for ongoing review.

5.3. Benign tumour outcomes

While the literature and local data collected as part of the St Jude studies show clear needs for neuropsychological support for the malignant brain tumour group (mainly medulloblastoma (PNET), ependymoma, atypical teratoid rhabdoid tumours and germinomas), service provision for children treated for benign brain tumours has been variable due to a lack of clear knowledge on neurocognitive risk for this population. In 2009-10, the RCH psycho-oncology research team conducted an initial pilot study on local brain tumour survivors examining neurocognitive outcomes (focused on attention skills) and brain changes using MRI. Two patient brain tumour groups, those undergoing surgery plus radiation and those with surgery only, were compared to healthy controls matched to cover the age and gender distributions of the clinical sample (Table 7).

Table 7: Means, standard deviations and range for demographic characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Surgery + Radiation (n=6)</th>
<th>Surgery (n=11)</th>
<th>Controls (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>2 male:4 female</td>
<td>6 male:5 female</td>
<td>5 male:8 female</td>
</tr>
<tr>
<td>Mean Age at time of assessment (Years)</td>
<td>11.3 (2.1)</td>
<td>10.1 (3.1)</td>
<td>10.8 (2.7)</td>
</tr>
<tr>
<td></td>
<td>7.4-13.8</td>
<td>6.6-17.4</td>
<td>7.4-16.1</td>
</tr>
<tr>
<td>Mean Age at diagnosis (Years)</td>
<td>7.3 (2.4)</td>
<td>6.8 (3.6)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>2.6-9.3</td>
<td>1.3-14.5</td>
<td></td>
</tr>
<tr>
<td>Mean Time since diagnosis (Years)</td>
<td>4 (0.8)</td>
<td>3.3 (1.3)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>2.8-4.9</td>
<td>1.9-5.7</td>
<td></td>
</tr>
<tr>
<td>Mean time since surgery (Years)</td>
<td>4 (0.8)</td>
<td>3.4 (1.2)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>2.8-4.8</td>
<td>2.2-5.7</td>
<td></td>
</tr>
</tbody>
</table>

Consistent with the research literature, children treated with CRT for a malignant tumour displayed significantly reduced performance on IQ, verbal intellectual skills, selective attention, rapid naming and information processing speed tasks when compared to healthy controls (Table 8). Comparable differences in IQ and processing speed were observed for the benign tumour group, with a trend towards reduced performances on attention tasks when compared to healthy peers. Of note, the surgery + radiation group only differed to the surgery group on a rapid naming task.
Table 8: Means, standard deviations and comparisons for neurocognitive outcomes

<table>
<thead>
<tr>
<th>Test</th>
<th>Construct</th>
<th>Surgery + Radiation (malignant)</th>
<th>Surgery (benign)</th>
<th>Controls</th>
<th>P-value</th>
<th>Eta squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>WISC-IV (mean=100, SD =15)</td>
<td>FSIQ</td>
<td>92.33 (10.33)</td>
<td>95.82 (11.59)</td>
<td>109.15 (11.72)</td>
<td>.006*</td>
<td>.313</td>
</tr>
<tr>
<td></td>
<td>VCI</td>
<td>89.50 (8.19)</td>
<td>95.82 (10.60)</td>
<td>103.54 (12.64)</td>
<td>.043*</td>
<td>.208</td>
</tr>
<tr>
<td></td>
<td>PRI</td>
<td>98.17 (13.95)</td>
<td>97.64 (11.17)</td>
<td>109.23 (15.99)</td>
<td>.105</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WMI</td>
<td>100.33 (16.60)</td>
<td>99.82 (10.18)</td>
<td>106.54 (10.05)</td>
<td>.324</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PSI</td>
<td>86.67 (8.50)</td>
<td>94.00 (12.03)</td>
<td>108.85 (11.15)</td>
<td>.001**</td>
<td>.426</td>
</tr>
<tr>
<td>TEA-Ch (mean=10, SD = 3)</td>
<td>Sustained</td>
<td>7.37 (2.97)</td>
<td>8.24 (2.35)</td>
<td>10 (1.92)</td>
<td>.055</td>
<td>.194</td>
</tr>
<tr>
<td></td>
<td>Selective</td>
<td>5.83 (1.60)</td>
<td>7.86 (2.23)</td>
<td>9.35 (1.49)</td>
<td>.002*</td>
<td>.367</td>
</tr>
<tr>
<td></td>
<td>Attention Control</td>
<td>7.83 (1.49)</td>
<td>8.33 (2.31)</td>
<td>9.82 (1.50)</td>
<td>.059</td>
<td>.189</td>
</tr>
<tr>
<td></td>
<td>Same World</td>
<td>5.00 (2.19)</td>
<td>8.91 (2.77)</td>
<td>10.00 (1.35)</td>
<td>.000**</td>
<td>.459</td>
</tr>
</tbody>
</table>

*p<.05
**p<.001

Results from the MRI component of the study demonstrated altered brain pathology in children from both clinical groups. The surgery + radiation group were found to have less grey matter in the thalamus bilaterally than healthy controls, while the surgery group had less grey matter in the right frontal gyrus and cuneus/precuneus regions than controls. Neither group showed differences in white matter brain volume, however diffusion weighted imaging (a technique looking at the integrity of white matter tracts) identified widespread differences centred around the corpus callosum, cortico-spinal tracts and thalamic radiation for both patient groups when compared to healthy peers (Figure 1).

Figure 1: Significantly increased mean diffusivity (seen in red) in surgery + radiation group compared to controls.

These findings support the clinical observation that children treated for a brain tumour represent an at-risk population for cognitive late effects even without the use of neurotoxic treatments such as CRT. While the profile of deficits may be similar to that for the CRT group for PF tumours, the trajectory of change for the benign tumour group remains unclear making review and discharge...
planning difficult. However, servicing all children treated for a brain tumour within an acquired brain injury framework presented a significant challenge under the existing service model.

5.4. Baseline assessment and beyond

In 2000, a prospective, longitudinal study of cognitive outcomes in 35 patients treated for a posterior fossa tumour was undertaken at the RCH. This study looked specifically at neurocognitive performance patterns over a period of 3 years post diagnosis. The results indicated an uneven trajectory of change for children treated with CRT and those treated with surgery only. Patients treated for a malignant tumour displayed decline in performance over the first 12 months, followed by some recovery of function in the second year, but later decline in the third year post-treatment [91](Figure 2). Change profiles remained stable for children treated for a benign tumour as a group, but individual trajectories demonstrated considerable variation between assessment time-points [91].

**Figure 2:** IQ performance profile for malignant tumour patients over a 4-year period

This research confirms findings in the literature of extended changes in developmental profiles over a number of years. While studies such as that by Palmer (2001) suggest a plateau in loss of IQ points after 6 years post-treatment [46], the absence of longitudinal studies beyond this time period make it difficult to interpret the generalisability of these findings.

These studies highlight the need for ongoing monitoring well into the long term follow-up period. They also highlight the importance of having well-trained, specialised clinicians to undertake assessments and interpret neurocognitive performance in a late effects framework given the multiple factors contributing to neuropsychological outcomes and the appearance of recovery early in the post-treatment period which may be misleading with respect to longer term neurocognitive performance.
5.5. Screening

Structured neuropsychological review schedules for at-risk patients have proven difficult in a service with limited capacity. With an accumulating cohort of patients, ways to screen for change in performance were investigated. In 2008, the RCH psycho-oncology research team undertook an audit of clinical assessment data to evaluate the utility of parent report as a screening method for neurobehavioural difficulties in paediatric cancer patients (poster, SIOP 2008). Assessments for 60 children (80% treated for a brain tumour) were analysed to compare parent ratings on the Behavior Assessment System for Children – Version 2 (BASC2) and the BRIEF with formal neuropsychological testing. Findings suggested that these parent-report questionnaires may be useful at identifying children with significant attention and cognitive deficits who require immediate intervention, as well as those children who are cognitively intact. In contrast, ability to identify subtle problems in this population of children based upon these parent-report questionnaires was poor. This was not surprising from a clinical perspective as mild attention problems are often obscured in everyday activities that parents observe, and more commonly are reported as fluctuating memory deficits during learning activities at school. It was concluded that the BASC2 and BRIEF may have a role in prioritising neuropsychological assessment for patients with childhood cancer, but that parent report was not sufficient as a screening tool to determine risk of mild to moderate cognitive difficulties. Furthermore, in a latter study it was found the correspondence between parent and child ratings of problem behaviours and emotional issues to be discrepant for some aspects of mental health, with adolescents reporting more problems than their parents and children under 12 years reporting fewer. These findings raised concerns regarding a service model which places significant weight on parent complaint as a trigger for neuropsychological review in the brain tumour group and as the basis for activating neuropsychological involvement for other diagnoses.

The need for a practical neuropsychological screening assessment was highlighted as a key requirement to deal with increasing pressure on the clinical service and to ensure patients with significant need would not be missed. With the release of the 2008-2011 Victorian Cancer Action Plan (VCAP) the need to screen for supportive care needs of cancer patients was formalised. The VCAP target to “aim to document supportive care screening for 50% of newly diagnosed cancer patients by 2012” highlighted the accumulation of research findings of increased need in this population and under servicing. Local research focus aligned well with this approach and a study was commenced to determine the rate of neurocognitive deficits in the local cancer population and the utility of a neurobehavioural screening assessment in the clinical setting.

A theoretically-derived battery of clinical neuropsychological measures that targeted cognitive areas most vulnerable to cancer treatments was developed. The screen (Trackwell) was applied in a survivorship cohort of children 1 to 6 years post-treatment and a newly diagnosed cohort of children who were approximately 5-weeks post-diagnosis. Cancer types treated with CNS-directed therapy in the form of brain surgery, CRT or MTX which included children treated for a brain tumour, leukaemia, lymphoma or osteosarcoma were targeted. The composition of the survivorship group is provided in Table 9. Findings from this group suggested that approximately 30-40% of children treated with CNS-directed therapy at the RCH or MCH are performing below age appropriate
standards across information processing, academic and visuo-motor integration domains (Table 10). This represents a substantial increase compared to the 15% expected from normal population data.

**Table 9: Trackwell Study - Survivor group demographics**

<table>
<thead>
<tr>
<th></th>
<th>Survivors N=137</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years post treatment</td>
<td>3.36 (1.22) 1-5:11 years</td>
</tr>
<tr>
<td>Mean Age</td>
<td>10.78 (3.90) 3-18 yrs</td>
</tr>
<tr>
<td>Gender</td>
<td>54.4% female</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>n=86 leukaemia, n=22 brain tumour n=22 lymphoma, n=3 osteosarcoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Controls N=67</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>10.99 (3.96) 3-18 yrs</td>
</tr>
<tr>
<td>Gender</td>
<td>56.7% female</td>
</tr>
</tbody>
</table>

**Table 10: Neurobehavioural profile of the Trackwell Survivorship Cohort**

<table>
<thead>
<tr>
<th>Cognitive Composite</th>
<th>Superior %</th>
<th>Above Average %</th>
<th>Average %</th>
<th>Below Average %</th>
<th>Extremely Low %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(2.1)</td>
<td>(13.6)</td>
<td>(66.8)</td>
<td>(13.6)</td>
<td>(2.1)</td>
</tr>
<tr>
<td>Visuomotor Integration</td>
<td>0.7</td>
<td>5.6</td>
<td>56.3</td>
<td>27.8</td>
<td>9.7</td>
</tr>
<tr>
<td>Information Processing</td>
<td>0.7</td>
<td>5.3</td>
<td>74.7</td>
<td>16</td>
<td>3.3</td>
</tr>
<tr>
<td>Working Memory</td>
<td>3.8</td>
<td>10.6</td>
<td>55.3</td>
<td>25.8</td>
<td>4.5</td>
</tr>
<tr>
<td>Selective Attention</td>
<td>0.7</td>
<td>4.6</td>
<td>70.2</td>
<td>19.9</td>
<td>4.6</td>
</tr>
<tr>
<td>Reading</td>
<td>1.3</td>
<td>7.3</td>
<td>69.5</td>
<td>16.6</td>
<td>5.3</td>
</tr>
<tr>
<td>Spelling</td>
<td>0</td>
<td>9.5</td>
<td>64.6</td>
<td>21.8</td>
<td>4.1</td>
</tr>
<tr>
<td>Mathematics</td>
<td>1.4</td>
<td>8.8</td>
<td>54.7</td>
<td>26.4</td>
<td>8.8</td>
</tr>
</tbody>
</table>

The brain tumour and blood cancer (leukaemia and lymphoma) survivors were analysed separately to better understand the needs of these 2 groups that make up the majority of referrals to the clinical service. Surprisingly, similar rates of deficit in core information processing skills and visuo-motor integration were seen for both groups, with an overrepresentation of children in the below average and extremely low ranges and an almost absence of children performing above average standards (Figure 3). Academic deficits were also elevated with approximately one third of both the brain tumour and ALL samples performing below the national average.
While deficit rates were expected to be high in the brain tumour population, similar rates of deficit in the blood cancer group were of significant concern. Analysis was undertaken to explore the relationship of treatment and patient variables with poor cognitive outcomes in the largest of the blood cancer groups, ALL. The use of high dose MTX, time since treatment or age at treatment were not found to be significant predictors of cognitive outcome. Age at assessment and gender were also not significant predictors.

The absence of sensitive indicators of vulnerability to the development of neurobehavioural late effects strengthened the argument for a screening measure that could be implemented at multiple time points to monitor change in developmental trajectories for a growing population of survivors. As part of the Trackwell project, a screen was applied to a newly diagnosed cohort of children to characterise cognitive profiles at diagnosis and determine the feasibility of administering a neurobehavioural assessment close to treatment commencement. No significant differences were observed between mean performance scores of the brain tumour group, non-CNS group (leukaemia, lymphoma or osteosarcoma) and healthy matched controls on cognitive or academic measures. As would be expected, when looking at the proportion of children performing below the average range, the brain tumour group showed high rates of deficit on visuo-motor tasks than controls, and poorer verbal fluency than the non-CNS group. However for both the brain tumour and blood cancer groups the proportion of children in the impaired range of functioning was much smaller than that observed in the survivorship cohorts of the same diagnoses, confirming that treatments are disrupting brain development in the long term.

In regards to feasibility, the mean time from diagnosis to assessment with the screen was 5.17 weeks and assessments were completed in under an hour for 87% of patients. Participant and
researcher evaluation indicated the screen was acceptable across a range of criteria, with no differences between clinical and control groups. Furthermore, compared to standard medical record documentation, the screen provided significant additional information on the developmental and neurobehavioral status of patients at diagnosis. These findings support the Trackwell screening assessment as a sensitive, brief, and cost-effective way of providing a gold-standard service of neuropsychological monitoring to a large, and growing, group of patients.

This approach is supported by the Children’s Oncology Group (COG) who has implemented a brief neuropsychological battery as the core component to all their studies looking at long-term cognitive outcomes following childhood cancer.
A framework for the future: acute and long term neuropsychology practices to ensure quality care for childhood cancer patients

Priority groupings: The ability to predict which children will suffer ongoing disease burden in the form of neurocognitive late effects is crucial to successful life outcomes. Individual variation following treatment has precluded the establishment of a risk algorithm to accurately identify which children will experience an adverse response. Factors that have been associated with poorer outcomes following CRT or MTX exposure include: (i) younger age at treatment [92] (ii) increased time since treatment [93] (iii) female gender [94] and (iv) higher doses [95] (Figure 1). For MTX, the cumulative dose and infusion rates may also be important in determining risk [95, 96]. Unfortunately in cases where differences are found, patient and treatment factors account for small amounts of variance in performance, suggesting that other host, disease or treatment factors, or complex interactions between known risk factors, may contribute largely to determining risk status.

Several factors must therefore be considered when proposing a model of care to adequately identify and intervene for children at risk, but not over-service the population:

- Many children who survive into adulthood will ultimately do well
- There remains significant uncertainty in anticipating long-term outcomes for individual patients
- Neuropsychological resources are limited but should not only service children at the top of the risk pyramid.

6. Service capability framework from diagnosis to long term follow-up

A service capability framework outlines minimum requirements and would meet the needs of patients at ‘high’ risk of cognitive late effects.

6.1. Acute services

*Children <3 years old:* Any patient aged < 3 years old at treatment should be seen at diagnosis for a developmental assessment and ongoing review. These children are classified as high risk regardless of diagnosis or length of treatment. This is a crucial period for brain development that is significantly driven by exposure to healthy social relationships and environmental stimulation. Any considerable interruption to normal life experiences during this time may result in regression of functional capabilities and/or delayed acquisition of developmental milestones. These children are more likely to demonstrate reduced intellectual ability and significant learning deficits over time and require long-term surveillance, and whenever possible early intervention. Review assessments may occur at various time-points (e.g. 6 months following baseline assessment) depending on the skills being monitored and the developmental stage of the child.

*Brain tumour:* All patients diagnosed with a brain tumour should be seen for baseline assessment (at diagnosis or as soon as possible post-surgery) and a minimum of 1 review. The long-term effects of a space occupying tumour and neurosurgery on an immature brain are well known and suggest that
even benign tumours can cause significant long-term damage depending on tumour, peri-operative and host factors. Children under 8 years of age are considered a higher risk classification than older children, and would therefore be expected to receive a further review assessment (generally around 24-months post-treatment) to monitor developmental trajectories.

* **Liquids:** ALL and non-Hodgkin’s Lymphoma patients on high-risk protocols, and AML patients, should be seen routinely at baseline and reviewed at the end of treatment. The use of MTX and ara-C as part of these protocols place a substantial number of these children at significant risk of neurocognitive late effects. Some patients may require an additional assessment during treatment depending on their response to treatment and length of school absence.

Children with **HLH that requires BMT** should be seen for a brief baseline assessment and then reviewed 6 months post-transplant, and a further 12 months post the initial review.

* **Any diagnosis:**
  * **CRT:** In addition, patients with any diagnosis that will undergo CRT > 14Gy should be seen at baseline, 12-months and 24-months post-diagnosis/treatment. This would include children having TBI for BMT that have a cumulative dose of radiation > 14Gy.

Any children 8 years or younger undergoing TBI would be considered at increased risk of neurological changes following CRT and should be seen for a brief baseline assessment and then reviewed 6 months post-transplant, and a further 12 months post the initial review.

When possible the baseline assessment for children undergoing CRT should occur pre-radiation and follow up should be no more than 2 years apart. CRT is a proven neurotoxin that damages healthy brain tissue and can result in very significant cognitive impairment that requires timely intervention. Serial assessment is required to monitor patterns of change in neurobehavioural development.

* **Ommaya reservoir:** Any child who will receive chemotherapy through an Ommaya reservoir should be seen for baseline assessment before the commencement of treatment and for a 12- and 24-month post-treatment review.

Any child who experiences a **CNS adverse event** (e.g. meningitis, posterior fossa syndrome, hydrocephalus, acute chemotherapy toxicity) should be seen as soon as possible after the event, and provided with a 12 and 24-month review post-event.

Any child who displays a **significant change in behavior**, memory/attention skills, or academic performance that is not clearly related to a situational or psychological issue should be seen immediately for assessment. The need for review/s will be determined on a case-by-case basis.

Any child with a **pre-existing developmental disorder**, history of significant developmental delay or diagnosed intellectual/learning disability should be referred to the service. The clinical team will then determine the need for assessment and follow-up depending on government and private services the child may already be accessing. It is expected that these children will receive a minimum
of 1 assessment during their treatment phase and a review at an appropriate time. Specialist consultation to alternative services would also be considered routine for these patients.

6.2. Long Term Follow-up Program

A Neuropsychologist should be present at all LTFP multidisciplinary (MD) new diagnosis and MD follow-up clinics to assess and determine the ongoing needs of patients. Specialist services outside of clinic times should also be provided to children at high-risk of cognitive late effects. These groups are outlined below.

Children who were diagnosed <3 years old: These children should be reviewed on entry to the service, and seen yearly for review assessment/monitoring until the time they are discharged. A discharge review and liaison with adult services is considered a priority for this group.

Brain tumour: Any child treated for a brain tumour who displayed significant neurobehavioural difficulties or a substantial change in performance over time on formal assessment should be provided with an assessment on entry to the service when an assessment has not been performed in the previous 12 months, and their ongoing needs monitored through LTFP clinics with the option for further input if required.

Patients who were treated for a supratentorial tumour, brainstem tumour, or inoperable tumour should be provided with the option of an annual review until discharged from the service. A discharge review and liaison with adult services may also be required for some of these patients.

Liquids:
ALL-HR, AML and NHL patients should receive a review assessment on entry to the service when an assessment has not been performed in the previous 12 months. Requirements for follow-up can then be determined. The service should also have capacity inbuilt to accommodate a proportion of these children (likely to be approximately 30%) for re-assessment if difficulties are present on assessment or are identified at a LTFP clinic.

Children with HLH that required BMT should be seen on entry to the service when an assessment has not been performed in the previous 12 months, and for a review at 12 or 24-months post. The need for ongoing input should be determined on the basis of the child’s performance/needs.

Any diagnosis:
*CRT: Any patient who received CRT >14 Gy should be reviewed on entry to the service when an assessment has not been performed in the previous 12 months (this would include children undergoing TBI with a cumulative dose > 14 Gy). For those displaying difficulties or significant change on assessment a review should be provided at 12 or 24-months post-review. Ongoing needs of all patients should be monitored through clinics.
Patients who received CRT > 25 gy should be seen annually for assessment up to 5 years post-diagnosis/treatment. Ongoing involvement may be required post this time and should be determined on a case-by-case basis. Assessment at transition times and/or periods of major cognitive development should also be provided as necessary. A discharge review and liaison with adult services is considered a priority for this group.

Children 8 years and under who received TBI for a BMT should be seen on entry to the service when an assessment has not been performed in the previous 12 months and followed through regular clinic appointments to determine the need for further follow-up.

* Ommaya reservoir: Patients who received chemotherapy through an Ommaya reservoir should be reviewed on entry to the service when an assessment has not been performed in the previous 12 months. For those displaying difficulties or significant change on assessment a review should be provided at 12 or 24-months post-review. Ongoing needs of all patients should be monitored through clinics.

Any child with a history of a CNS adverse event should receive an assessment on entry to the service when an assessment has not been performed in the previous 12 months and a review at 2-years post entry (or post last assessment). The requirement for further follow-up can then be determined.

Any child who displays a significant change in behavior, memory/attention skills, or academic performance that is not clearly related to a situational or psychological issue should be seen immediately for assessment. The need for review/s will be determined on a case-by-case basis.

Any child with a pre-existing history of developmental disorder, significant developmental delay or diagnosed intellectual/learning disability should be referred to the service on entry to LTFU. The ongoing needs of these patients will then be determined by the clinical team.

* Yearly reviews need not consist of a comprehensive formal assessment at all time-points, however a formal process of review external to the LFTP clinics is considered necessary to ensure that relevant cognitive areas are adequately explored and appropriate assessment occurs.

6.3. Clinical trial requirements

For patients enrolled on, or following, a clinical trial that includes neuropsychological evaluation, the requirements of the study will be the responsibility of the CRF coordinating the trial. Where clinical trial compliance and clinical needs match, every effort will be made to align these assessments to minimise burden on patients and families. Any additional clinical trial requirements (e.g. repeat administration of specific measures, QoL questionnaires etc.) that are not considered standard of care for the service are considered outside of the service model provided and will need to be covered by the clinical trial budget.
7. Optimum care pathway from diagnosis to discharge

In addition to the service capability framework, an optimum care pathway would utilise the COG guidelines, and combine them with screening protocols for children at moderate risk of treatment-related changes to neurobehavioural development, in addition to providing the opportunity for specialist intervention planning for those children with the most significant alterations to cognitive capacity.

7.1. Acute service

Liquids: Neuropsychological screening should be provided for all leukaemia patients at diagnosis, commencement of maintenance therapy and end of treatment. Screening should also be provided for all patients diagnosed with NHL and osteosarcoma at diagnosis, and end of treatment.

BMT: Neuropsychological screening of all children who are to undergo a BMT should be offered. Patients should then be reviewed at 6-months post BMT and then 12-months following the first review.

Solid tumours: Any child with a rhabdomyosarcoma of the eye socket or skull should be seen for formal assessment and provided with a minimum of 1 review.

Intervention: The Neuropsychology service should have inbuilt capacity to provide school visits, learning plans, behavior management training, psycho-education, support intern-training programs and research.

7.2. Long Term Follow-up Program

All groups seen by the acute service (leukaemias, NHL, osteosarcoma, rhabdomyosarcoma) should be seen for a review (screening assessment) on entry to the LTFP. Patients can then be monitored for ongoing needs through the clinics and provided with assessment as required.

BMT: Patients who underwent a BMT should receive a routine review at 24-months post-entry to the service in addition to the above screening assessments.
8. Assessment schedule

8.1. Service capability framework

Table 11: Assessment schedule for service capability framework

<table>
<thead>
<tr>
<th>Group</th>
<th>ACUTE Service</th>
<th>Interim Review</th>
<th>LTFRP</th>
<th>Entry</th>
<th>Clinic Review</th>
<th>Yearly</th>
<th>At Discharge</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>1 Review</td>
<td>2 Review</td>
<td>Entry</td>
<td>Clinic Review</td>
<td>Yearly</td>
<td>At Discharge</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
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<td>ALL-HR NHL</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>CRT ≥ 14Gy</td>
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</tr>
<tr>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tr>
<tr>
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<td>✓</td>
</tr>
<tr>
<td>TBI ≤ 8yo</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CNS adverse event</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>Significant change</td>
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<td>On needs basis</td>
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<td>✓</td>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>History of developmental/learning disorder</td>
<td>✓</td>
<td>✓</td>
<td>On needs basis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

8.2. Optimum care pathway

As outlined in Table 11, with the addition of the below screening assessments.

Table 12: Assessment schedule for optimum care pathway, including screening assessments

<table>
<thead>
<tr>
<th>Group</th>
<th>ACUTE Service</th>
<th>Interim Review</th>
<th>LTFRP</th>
<th>Entry</th>
<th>Clinic Review</th>
<th>1 Review</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Baseline</td>
<td>On-treatment</td>
<td>End of treatment</td>
<td>Entry</td>
<td>Clinic Review</td>
<td>1 Review</td>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NHL</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Osteosarcoma</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>All BMT</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Rhabdomyosarcoma (eye socket/skull)</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Recommended future research directions

Neurobehavioural deficits are a core feature of life for a significant proportion of Victorian childhood cancer survivors. As outlined in the previous sections, building an optimum care pathway for neuropsychological services requires clinical expertise, appropriate monitoring and assessment of at-risk patients. In addition, the program should have an inbuilt research arm that allows for the development and implementation of complementary studies that inform, assess and enhance the clinical service. As with other professional clinical models, a strong research focus is best supported by developing staff positions with dual roles in research and clinical fields.

The current psycho-oncology service has a strong history in research and this has been crucial in developing and refining the existing service. For example, the CCC psycho-oncology research group is currently conducting a longitudinal study of neurocognitive outcomes following ALL treatment that is exploring the proposed moderating role of genetic factors in determining the vulnerability of patients to the risk factors described above [97, 98]. In particular, differences in the patient’s genetic background, through single nucleotide polymorphisms (SNPs), are thought to contribute significantly to the observed variability in long-term outcomes following exposure to neurotoxic treatments. The research hopes to elucidate this relationship between constitutional factors and cognitive/neurological outcomes to allow for close neuropsychological monitoring of patients on the basis of genetic risk and their possible allocation to lower risk treatment arms to avoid significant neurocognitive late effects.

The ultimate goal of this research and other studies in the neurocognitive field is the development of proactive, individualised intervention programs. The lack of well defined, specialised intervention or remediation programs for this population represents a significant gap and is an area that needs to be developed in order to avoid the cumulative effects of neurobehavioural difficulties on development and quality of life for survivors. A well designed, serial assessment clinical program would provide crucial data to inform such programs and contribute significantly to the local and international paediatric cancer field.

In addition to local research endeavours, the number of patients on multiple clinical trials who come under the care of the clinical service requires research expertise to direct and coordinate the neurocognitive requirements of several studies. Having staff with research training allows for the team to ensure that patients’ needs are met whilst contributing to advances in patient care for the wider paediatric cancer population.
Key recommendations

The recommendations of this report are based on review of the international literature and guidelines for neurobehavioural services, and informed by Victorian research data.

The recommendations are as follows:

- The Children’s Oncology Group (COG) guidelines for long term follow-up of childhood cancer patients provide clear directives for neuropsychology service development that should be incorporated into our local program.
- Research and quality review should be in-built to the program to allow for ongoing evaluation of local needs and to inform the development of customised intervention programs. The success of this approach lies in developing joint positions for staff in both clinical and research programs. This will ensure the successful implementation of studies across acute and LTFP services, and to the translation of research findings into quality improvements in the clinical service.
- Future goals should include the development and implementation of proactive intervention services that are tailored to the local survivor population.
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