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(2018)

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*Journal of Adolescent and Young Adult Oncology*, 7(1), pp. 37-45.

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<https://doi.org/10.1089/jayao.2017.0042>

## **Improvements in clinical practice for fertility preservation amongst young cancer patients: results from bundled interventions**

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**Running head:** *Improvements in clinical practice for fertility preservation*

**Key Words:** *fertility preservation; oncofertility; interventions; quality improvement; documentation*

## ***Abstract***

**Purpose:** The consequences of cancer and treatment on fertility can be a continuing source of distress for adolescents and young adults. The study aims were to assess the effects of bundled interventions on clinical practice concerning fertility in young people aged 14-25 years with cancer.

**Methods:** Bundled interventions, including development of quality indicators, resources and targeted education, were introduced during 2015 across five cancer centres. Data prior to interventions (2012-2014) was compared with data prospectively collected during 2015-2016. Relative Risks (RR) with 95% Confidence Intervals (CI) were calculated to assess effects of interventions.

**Results:** Compared with the pre-intervention cohort (n=260), the post-intervention cohort (n=216) were 1.47 times more likely to have documented discussion of risk of infertility (95% CI 1.12-1.63,  $p < 0.001$ ). Similarly, documented referral to fertility specialists was more likely in the post-intervention cohort (RR 1.53, 95% CI 1.26-1.87,  $p < 0.001$ ) as was documented fertility preservation outcomes (RR 2.56, 95% CI 1.91-3.44,  $p < 0.001$ ). These differences were significant across age, gender and diseases. Females had greater improvement in documented risk of infertility discussion between cohorts (RR 1.70, 95% CI 1.19-2.08,  $p < 0.001$ ). Amongst diseases, the greatest improvements were seen in those with brain cancers (RR 2.15, 95% CI 1.28-3.62,  $p = 0.004$ ) and soft tissue sarcoma (RR 2.60, 95% CI 1.17-5.78,  $p = 0.02$ ).

**Conclusions:** We have demonstrated the effects of bundled interventions to improve clinical practice associated with fertility preservation in young people with cancer. Interventions were successful for reducing disparities identified in the pre-intervention cohort associated with

gender and certain diseases. Assessment of the quality of patient care is not possible without accurate, consistent documentation.

## ***Introduction***

With the advances in cancer treatment and management, attention now includes a focus on the long-term quality of life after cancer treatment. The effects of treatment on fertility are a great concern to many young people. For some the loss of a future child may be more distressing than a cancer diagnosis itself,<sup>1</sup> and indeed, a cancer diagnosis does not change the desire for biological children.<sup>2</sup> Young people may experience distress and regret if not provided the opportunity to discuss the risks of infertility and to preserve fertility where possible.<sup>3</sup> Consultation with fertility specialists before the initiation of cancer treatment offers the potential to optimise the potential of becoming biological parents in the future, and minimise the effects of fertility impairment on quality of life.<sup>4,5</sup> Governing bodies recommend all newly diagnosed cancer patients of reproductive age are informed about their fertility preservation options, and that those who express an interest are referred to fertility specialists.<sup>6-8</sup> Despite these recommendations, numerous studies have identified that the risk of infertility is not routinely discussed in clinical practice, and that when it is, it does not occur in an optimal way, at the optimal time or with the patient as part of planning cancer treatment.<sup>5,9-13</sup>

During adolescence and young adulthood, clinicians may be uncertain about how involved young people should be in treatment decisions, and clinicians report discomfort with discussing the potential effects of treatment on fertility.<sup>12</sup> Moreover, research demonstrates both disparities with gender and; male and older patients are reported to receive more information compared to female and younger patients.<sup>12</sup> As a result, young people may not receive appropriate information and they describe feeling distressed and confused about the potential consequences of cancer treatment on their fertility.<sup>10,14,15</sup> While disparities between gender and age are well described, little is understood regarding differences due to diagnosis and whether this is an also important factor.<sup>12</sup>

From the clinician's perspective, there can be medico-legal consequences if a patient feels they have received inadequate information. In 2014, there was successful action against a health service for failing to provide information regarding options for fertility preservation to a 14 year old male prior to treatment.<sup>16</sup> In this case, some six years after treatment completion, the patient's action against the health service was successful, and the health service was found to have "breached consumer rights for failing to have adequate mechanisms in place to ensure the provision of fertility information and treatment options to consumers prior to undertaking chemotherapy treatment".<sup>16</sup>

For these reasons, risk of infertility discussions should be clearly documented in the patient medical notes as a record of discussion between patient and clinician. The discussion and subsequent documentation provides important information about AYA understanding of the process, support received by health professionals and other sources of information provided.<sup>17</sup> Including the patient's GP in correspondence can facilitate appropriate follow-up of anticipated reproductive or sexual dysfunction concerns following treatment. This information is particularly useful to inform future family planning discussions between patients and clinicians.

The aim of this study was to investigate the effects of a bundle of interventions (described below) on the clinical practice of documenting risk of infertility discussion, referral for fertility preservation and outcomes of fertility preservation in young people aged 14-25 years undergoing cancer treatment. Secondary aims were to explore the variables associated with variation in practice regarding fertility preservation.

## ***Methods***

### **Setting**

The Youth Cancer Service (YCS) in Queensland, Australia, is a state-wide partnership model based across five tertiary cancer centres in the state. The Queensland YCS advocates all young people with a cancer diagnosis have access to verbal and written information regarding risks of infertility, and that fertility preservation options should be available to patients where clinically possible. Bundled interventions were introduced during 2015 across these five cancer centres. Data prior to interventions (2012-2014) was compared with data prospectively collected during 2015-2016.

### **Pre-intervention cohort**

To collect data prior to interventions, we undertook a retrospective medical record audit of adolescent and young adult (AYA) patients aged 14-25 years at the time of a cancer diagnosis between the years 2012-2014. A list of patients from each of the five cancer centres was obtained using ICD-10 codes for a cancer diagnosis associated with a hospital admission during the study period (2012-2014). All patients identified in the list were reviewed for eligibility for inclusion in the audit. Patients were included if they presented with a secondary cancer following a childhood cancer diagnosis, but excluded if they had relapsed disease that had been treated in the previous 5 years. Patients with a diagnosis of localised melanoma, or in situ carcinoma such (e.g. thyroid cancer) where systemic treatment was not required were also excluded from the study because there was no risk to fertility; these patients were also less likely to have been referred to youth cancer services.

The audits were undertaken at the five cancer centres associated with the YCS in Queensland, Australia. One hospital is a tertiary paediatric cancer centre in metropolitan Brisbane, two hospitals are tertiary adult cancer centres also located in Brisbane and the remaining two hospitals are adult cancer centres located in large regional centres. During the year 2013, three facilities moved to electronic medical records and patient paper medical records were archived.

Because of costs and time constraints, where patient medical records were not readily available for auditing, they were excluded from the study.

### **Instruments**

An audit tool was developed by the research team to extract data from the paper based or electronic medical record. Items included: patient demographics; age at diagnosis; diagnosis; treatment received; documented evidence of risk of infertility discussion; referral to fertility specialists; documented evidence of fertility preservation; details of fertility preservation efforts. Study co-ordinators at each site were trained to use the tool. The first three months of clinical notes following diagnosis, correspondence between service providers and chemotherapy administration sections of medical records were reviewed by study coordinators. Data were extracted and entered into a research database each site by the study coordinators and then collated for analysis.

### **Interventions**

Interventions to improve clinical practice of documented risk of infertility discussion and subsequent referral for fertility preservation consisted of multiple processes that were introduced during 2015. (Box 1)

### *Quality indicators*

At the commencement of 2015, performance metrics regarding fertility, as well as other indicators were included as part of YCS reporting. Collaboration with Queensland Cancer Control Analysis Team facilitated web-based data management of these indicators in a state-wide clinical database (Queensland Oncology OnLine - QOOL) for all patients. Cancer care co-ordinators in each of the five partner sites were responsible for prospectively entering patient information in the QOOL database following presentation of patients at multi-



disciplinary meetings. Dated metrics concerning the following fertility indicators were collected for each patient referred to the YCS:

- Was the patient provided with written and verbal information regarding fertility preservation options? (Yes/No)
- Was the patient referred to a fertility specialist? (Yes/No)
- Did the patient undergo fertility preservation (Yes/No)
- If Yes- What preservation method.

### *Targeted education*

Inter-professional Education sessions were based on learning needs survey undertaken in 2013 with 107 health professionals across all sites. Topics included fertility and genetics, communicating with AYAs; sexuality, intimacy and relationships; and fertility preservation methods for males and females. Education sessions consisted of a 30 minute presentation, provision of a fact sheet, resources including journal articles, websites and a print out of the presentation, and discussion of referral pathways. Education sessions were repeated regularly and delivered across all sites in small targeted groups to over 80 health professionals during 2015-2016.

### *Patient resources*

One of the barriers identified in the learning needs survey was a lack of accessible resources regarding fertility for patients in the inpatient areas of the hospitals. While clinicians were aware there were resources produced by various fertility and cancer support groups, not having these readily available prevented some clinicians from initiating discussions with a patient. Resource packs were therefore established for patients with gender specific information and brochures for fertility specialist groups. These packs were distributed to patients by the cancer care coordinators.

### *Referral processes*

Finally, referral pathways, procedures and work instruction forms were developed. Previously referral pathways had been rather informal, physicians may simply have telephoned a fertility specialist to make a referral, or write referral letter. It was observed at times that patients would not have all the required information when attending a specialist appointment. For example, a patient may not know the type, intensity of duration of planned treatment; unless this is included in the referral, the fertility specialist may need to seek further information. Additionally the referral form prompts clinicians to forward serology results regarding HIV, Hepatitis C and B and Syphilis status. Anecdotally, there were instances of avoidable delays due to incomplete information being provided to the fertility specialists. Having these processes agreed upon and documented, formalised the process and raised awareness to ensure all relevant information was collected and passed onto fertility specialists.

### **Post-intervention cohort**

Prospectively collected data post intervention were retrieved data on all patients entered into the QOOL database from the five cancer centres throughout 2015-2016. Dated quality indicators collected for patients regarding fertility included:

- Was the patient provided with written and verbal information regarding risks of infertility? Yes/No
- Was the patient referred to fertility specialist? Yes/No
- Did the patient undergo fertility preservation? Yes/No
- If yes- what was the fertility preservation method?

These indicators were extracted from the QOOL database along with patient details regarding demographics, age at diagnosis, diagnosis and treatment received. These data were used to evaluate the effects of the bundled interventions in the post-intervention cohort.

### **Data analysis**

Diseases were classified according to the AYA Cancer Classification Scheme.<sup>18</sup> Descriptive statistics were used to compare pre- and post-intervention patient cohorts for: age group (14-19 years and 20-25 years); gender; cancer diagnosis; type of treatment; toxicity of treatment on gonads; documented risk of infertility discussion, and documented fertility preservation outcomes. To establish the toxicity of treatment on gonads, we reviewed the chemotherapy type and dose, as well as any systemic radiotherapy treatment received by each patient. These data were reviewed against Levine's et. al. classification of effects of chemotherapy on sperm production or amenorrhea.<sup>19</sup> Accordingly, treatment was considered gonadotoxic if it was classified as a high or intermediate degree risk. Chi square tests were used to calculate statistical significance of characteristic differences between pre- and post-intervention cohorts. Relative Risks (RR) with 95% Confidence Intervals (CI) were then calculated between pre-and post-intervention cohorts to determine the difference between cohorts with 1) documented risk of infertility discussions, 2) referral to fertility specialists and 3) outcomes of fertility preservation. Finally, overall influence of gender, age and diagnosis on documented clinical practice regarding fertility was assessed in the post-intervention cohort.

### **Compliance with ethical standards**

Human Research Ethics Committee approval was obtained prior to commencement of the study (HREC /14/QRCH/364). Waiver of consent was approved for this low- and negligible risk research. All procedures performed in this study were in accordance with the ethical standards of the National Health and Medical Research Council.<sup>20</sup> The authors declare they have no conflicts of interest.

### **Results**

Of the 352 patients identified in the pre-intervention phase, 260 records were eligible for inclusion; records were not available to be retrieved for 23 patients, and 69 records were

excluded based on diseases not requiring systemic treatment affecting fertility (thyroid carcinoma  $n= 46$ , other in situ carcinoma  $n=20$ , melanoma  $n= 3$ ). For the post-intervention cohort, data were reviewed for all 216 patients' records. Characteristics of both patient cohorts are presented in Table 1. Characteristics of both cohorts for proportions of age group, sex and cancer diagnoses were comparable. Despite exclusion of diseases likely to require only localised treatment, there were significant differences between cohorts; patients in the pre-intervention cohort were more likely to be treated with surgery or localised radiotherapy and patients in the post-intervention cohort were more likely to be treated with chemotherapy or multi-modal therapy ( $p=0.006$ ). However, the toxicity of treatment on gonads was comparable between pre and post intervention cohorts with 75% and 78% respectively receiving intermediate to high risk treatment potentially effecting fertility.

## **Outcomes**

Compared to patients pre-intervention, the post-intervention cohort was significantly more likely to have: a) evidence of risk of infertility discussion (RR1.47, 95%CI 1.12-1.63  $p<0.001$ ); b) documented referral to fertility specialist (RR 1.53, 95% CI 1.26-1.87,  $p<0.001$ ), and c) documented fertility preservation outcomes (RR 2.56, 95% CI 1.19-3.44,  $p<0.001$ ). See Tables 2, 3 and 4.

## **Documented risk of infertility discussion**

Pre-intervention, we noted patients with lymphoma were the most likely (80%) to have documented risk of infertility discussion and patients diagnosed with soft tissue sarcoma were the least likely (28%). These findings were not associated with individual clinicians, teams or facilities; patients with both lymphoma and soft tissue sarcoma were represented across the

five study facilities. Post-intervention, a significant improvement in documented risk of fertility discussion was observed across all patient variables in both age groups, both males and females, and in all diseases except lymphoma (Table 2). Because patients with lymphoma in the pre-intervention cohort already had high documented risk of infertility discussion, the increase to 94% post interventions was not statistically significant.

The greatest improvement for documented risk of infertility discussion occurred in females (RR 1.7, 95% CI 1.39-2.08,  $p < 0.001$ ) and in patients with brain cancer (RR 2.15, 95% CI 1.28-3.62,  $p = 0.004$ ) and soft tissue sarcoma (RR 2.60, 95% CI 1.17-5.78,  $p = 0.02$ ).

### **Documented referral to fertility specialist**

The number of documented referrals to fertility specialist also improved significantly post-intervention across both age groups and for both males (RR 1.44, 95% CI 1.17- 1.77,  $p = 0.004$ ) and females (RR 1.82, 95% CI 1.15-2.89,  $p = 0.01$ ). Significant differences for this outcome were associated only with patients diagnosed with bone sarcoma (RR 1.84, 95% CI 1.12-3.01,  $p = 0.015$ ) and carcinoma (RR 2.37, 95% CI 1.15-4.88,  $p = 0.019$ ) (Table 3).

### **Documented fertility preservation outcomes**

Similarly, there were significant differences pre and post intervention in patient who underwent fertility preservation; both age groups and both males (RR 2.89, 95% CI 2.05-4.09,  $p < 0.001$ ) and females (RR 1.9, 95% CI 1.08-3.33,  $p = 0.025$ ) were significantly more likely to undergo fertility preservation in the post intervention cohort. Significant differences between diseases post intervention were noted for documented fertility preservation outcomes in patients with bone sarcoma (RR 3.08, 95% CI 1.32-7.18,  $p = 0.009$ ) and germ cell tumour (RR 2.71, 95% CI 1.37-5.38,  $p = 0.004$ ) (Table 4).

## **Influence of age, gender and disease on fertility preservation practices in post-intervention cohort**

Data for the post-intervention cohort were analysed to assess the influence of variables associated with the three outcomes of documented: risk of infertility discussion; referral to fertility specialist, and fertility preservation (Table 5).

### **Age**

As observed in the pre-intervention cohort, there were no significant differences associated with age categories for documented risk of infertility discussion or referral to fertility specialists; patients aged 14-19 years were comparable to patients aged 20-25 years. However, those aged 14-19 were 0.50 (95% CI 0.35-0.72,  $p=0.002$ ) times as likely compared to those aged 20-25 years to have documented outcomes of fertility preservation.

### **Gender**

There were significant differences associated with gender. Compared to females, in the pre-intervention cohort males were more likely to have documented risk of infertility discussion (RR 1.37, 95% CI 1.11-1.68,  $p=0.003$ ). This disparity closed in the post-intervention cohort with no significant differences identified between males and females post-intervention (RR 1.04, 95% CI 0.95-1.15,  $p=0.37$ ) for documented risk of infertility discussion. However, compared to females, males were still significantly more likely to be referred to fertility specialists (RR 1.83, 95% CI 1.37-2.46,  $p=0.001$ ), and to have documented fertility preservation outcomes (RR 2.06, 95% CI 1.44-2.96,  $p=0.001$ ).

### **Disease**

In the post-intervention cohort, the only disease with significantly different likelihood of documented discussion were germ cell tumours (RR 1.10, 95% CI 1.01-1.20,  $p=0.03$ ).

Documented risk of infertility discussion was otherwise comparable across other disease groups. Differences were noted in regards to referral to fertility specialists; patients diagnosed with acute leukaemias were less likely to be referred (RR 0.59, 95% CI 0.38-0.92, p=0.02) and those diagnosed with lymphoma and bone sarcomas were significantly more likely to be referred (RR 1.29, 95% CI 1.02-1.63, p=0.03 and RR 1.47, 95% CI 1.15-1.87, p=0.002 respectively). No differences were found with documented fertility preservation outcomes associated with disease.

The documented types of fertility preservation undertaken are presented in Figure 1. There were noticeable differences between years pre-intervention 2012-2014 and post intervention 2015-2016, particularly in regards to oocyte or embryo preservation and documentation of patients declining preservation. Sperm cryopreservation was the most common preservation method for males. A number of patients underwent multiple methods, e.g. combinations of oocyte/ embryo cryopreservation and ovarian suppression.

### ***Discussion***

To the best of our knowledge, this is the first multi-centre study examining the effects of bundled interventions on documentation for risk of infertility discussion, fertility referral and fertility preservation outcomes in AYA patients with cancer. The study identified existing disparities between gender and disease were closed with the introduction of interventions that included: streamlined referral pathways, education focus on fertility, and distribution of patient resources and the recording of quality indicators for clinical practice with fertility. This study contributes new information regarding differences associated with gender, age and disease, and adds to the small body of evidence regarding the clinical practice of risk of infertility discussion and interventions for fertility preservation in AYA cancer.<sup>12</sup>

Unlike previous studies reporting clear disparities associated with age,<sup>21,22</sup> we found no significant differences with documentation of risk of infertility discussion, or referral to fertility specialist associated with age in both the pre and the post intervention cohort. Other studies have suggested younger patients may not consider their fertility to the same extent as older patients, as it can be difficult to comprehend how fertility may impact upon their future lives.<sup>23,24</sup> Current practice at the YCS affiliated paediatric hospital is to aim to discuss fertility issues openly with both the patients and parents in all cases. This is likely to have contributed to the documentation of such discussions in this facility, such that we found no differences between patients aged 14-19 years and those who were aged 20-25 years who received treatment in adult cancer centres.

Similar to other reports in the literature,<sup>2,12</sup> we did find differences in both documentation of discussions, referral to fertility specialist and fertility preservation associated with gender, most noticeably in the pre-intervention cohort. While males were still more likely than females to have evidence of efforts made to preserve fertility, we were able to significantly reduce this disparity in the post intervention cohort. These findings provide possible solutions to eliminate gender disparities with clinical practice, facilitating more equitable care to all young people, and may also assist with the development of clinical guidelines.

Gender differences in fertility preservation are likely a consequence of the technicalities of fertility preservation. In males, sperm banking is a relatively simple, non-invasive procedure, and the success rate of achieving a live pregnancy with cryopreserved sperm is high. In females however, cryopreservation of oocytes is invasive, requires delay of treatment for at least two weeks, and a smaller proportion of oocytes survive the process of cryopreservation and thaw.

<sup>25</sup> It is also worth noting spermatogenesis takes approximately 74 days, whereas females are born with their full complement of oocytes at birth.<sup>26</sup> These differences have made fertility preservation difficult in females. While there is increasing evidence of the potential for ovarian



suppression and oocyte cryopreservation to be used in female fertility preservation, particularly in the pre-intervention cohort, these techniques were still considered experimental and not routinely advocated for.<sup>7,27</sup> However, while these technicalities may account for gender differences in rates of fertility preservation, they should not affect rates of risk of infertility discussion.

We were able to improve documentation of risk of infertility discussions across all disease types. Patients with lymphoma were the only disease type where significant differences were not found; this may be explained by the already high rate of risk of infertility discussion in the pre-intervention cohort. The high proportions of patients with lymphomas, bone sarcomas and germ cell tumours that went on to preserve fertility may be explained in part by having time to delay treatment. It is possible other patients may have been too ill to have undergone preservation, or that the severity of disease necessitated immediate commencement of treatment. The clinician's objective in most cases is to make a professional judgement regarding urgency of treatment, and assess the likelihood of successful preservation in an ill individual. It is well documented that spermatogenesis and the ability to ejaculate viable sperm are impaired when male patients are under stress.<sup>28</sup> It is conceivable clinicians considered discussions regarding future fertility were not considered appropriate. It should also be noted that documentation does not always reflect actual practice.<sup>29</sup> In our pre-intervention cohort there were five patients with lymphoma, treated with gonadotoxic treatment who did not have a documented risk of infertility discussion, but who did have documented fertility preservation outcomes- in most instances confirmation of sperm cryopreservation. These findings were not replicated in other diseases; however it is likely that rates of discussion were higher than rates of documentation.

The negative consequence of failing to provide patients with information has been documented in case studies.<sup>16</sup> The medico-legal risks justifies the importance of the current study, and

highlights the importance of completing and documenting a risk of infertility discussion, even if preservation is not carried out. However, it should also be considered that the outcomes of this study may be explained in part by the close juxtaposition between the legal case study in 2014 and our data collection before and after this time point. Clinicians may have had a heightened awareness of the potential for medico-legal consequences and thus have been more vigilant with documentation and clinical practice regarding risk of infertility in the post intervention cohort.

Nevertheless, the potential for these issues to arise has recently been highlighted in systematic reviews that appraised the quality and recommendations of clinical practice guidelines around the world for fertility preservation in cancer patients. The authors observed variability, poor quality and lack of uniformity across the guidelines and concluded these are likely to lead to conflicting recommendations and variation in clinical practice.<sup>12,30</sup>

The importance of the role of the clinician in discussions and decisions regarding fertility preservation cannot be underestimated. These discussions are highly significant for patients and parents.<sup>22</sup> Patients may be concerned about their fertility after cancer regardless of the types of treatment received.<sup>15</sup> Patients want information regarding risks; referral to fertility specialists has been highlighted as contributing to lower regret and greater quality of life for patients after cancer treatment<sup>3</sup> and with those who undergo fertility preservation believe they had made the right decision.<sup>23</sup>

Our study identified significant improvement in documentation of clinical practice in relation to fertility preservation, and anecdotally we also found evidence of multiple patients achieving pregnancy after cancer treatment. An important aspect of fertility counselling should include the re-assessment of fertility after treatment has completed. For males, this can include re-

assessment of sperm count and motility, and for women, a pre and a post-treatment blood test of anti-mullerian hormone can provide an indication of ovarian function.<sup>31</sup>

The issue of contraception is also important to consider; in this relatively small cohort of patients, two female became pregnant during treatment. Both women, one treated for Hodgkin's lymphoma and the other for an osteosarcoma, chose to continue their pregnancies. However, the disease in both women was unable to be controlled and both died in the second trimester of pregnancy. The difficult ethical dilemmas faced by both clinicians and patients in these cases highlight the importance of considering all aspects of fertility during cancer treatment.

### **Limitations**

The authors acknowledge the limitations of our findings due to the retrospective nature of pre-intervention cohort and reliance on medical records. Additionally our post-intervention cohort data was retrieved from QOOL - a state-wide clinical database- rather than the direct patient medical records; information in medical records may be different to that of the database. Nevertheless, our findings highlight the positive effects of relatively simple interventions to improve documentation of clinical practice. Further research is required to understand patient's health literacy of the risks of infertility due to cancer treatment and options for fertility preservation. While providing information is thought to be beneficial, little is known or understood about how this information is used by patients or if it is helpful. It is also not known if patients sought psychological support regarding fertility, or if patients received fertility referral and specialist consultation in a timely manner.

### **Conclusion**

With the high survival rates now achievable for many adolescents and young adults with cancer, issues such as fertility are increasingly important. We have demonstrated the success

of a bundle of interventions aimed at improving documentation of clinical practice related to fertility in young cancer patients. For various reasons, detailed in our study, it is imperative there is clear documentation of clinical discussions in patients' medical records. This ensures there is evidence that reflects the clinical advice and interventions provided to patients. To reduce variations in practice and improve quality of care, we recommend all cancer centres routinely record discussions regarding risk of infertility as a quality indicator. This study has not only provided a benchmark from which we can measure improvements, but also stimulated clinicians across multiple cancer centres to reflect upon clinical practice and to consider the importance of fertility for this population.

### **Acknowledgements**

We acknowledge the support of the Queensland Youth Cancer Service (QYCS), which receives federal funding through CanTeen as well as state and territory government funding, provide specialist, age-appropriate treatment and support for young cancer patients aged 15 - 25. We thank Glen Kennedy and Kirk Morris for their clinical advice, the QYCS Steering committee and the clinical staff of the QYCS for their contributions in undertaking this study. We also thank Shoni Philpot and Danica Cossio from the Queensland Cancer Control Analysis Team for their support with data management for the QYCS.

### **Disclaimer**

The authors declare no conflicts of interest. Findings from this work have been presented in poster format at local meetings at the Royal Brisbane and Women's Hospital and the Lady Cilento Children's Hospital in Brisbane, Australia. This work was also accepted for platform presentation at the Brisbane Cancer Conference and as a poster presentation at the Teenage Cancer Trust International conference in the UK 2016.

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Table 1

**Characteristics of patients ages 14-25 years with a cancer diagnosis before (N=260) and after (N=216) bundled interventions**

Variable	Pre-intervention N=260 %		Post intervention N=216 %		Chi square p value
Age at diagnosis					
14-19	121	47%	102	47%	p=0.96
20-25	139	53%	114	53%	
Gender					
Male	153	59%	128	59%	p=0.93
Female	107	41%	88	41%	
Cancer Diagnosis					
Leukaemia	50	19%	39	18%	p=0.46
Lymphoma	60	23%	63	29%	
Brain cancer	35	13%	23	11%	
Bone sarcoma	26	10%	27	13%	
Soft tissue sarcoma	18	7%	18	8%	
Germ cell tumour	37	14%	29	13%	
Carcinoma	24	9%	13	6%	
Other	10	4%	4	2%	
Type of treatment					
Multimodal	108	42%	96	44%	p=0.006
Chemotherapy only	104	40%	102	47%	
Surgery +/-localised radiotherapy	48	18%	18	8%	
Toxicity of treatment on gonads					
Intermediate to high risk	195	75%	168	78%	p=0.55
Low to no risk	65	25%	48	22%	
Evidence of risk of infertility discussion					
Yes	159	61%	194	89%	p=<0.001
No	101	39%	22	11%	
Documented fertility preservation outcomes					
Yes	93	36%	100	46%	p=0.02
No	167	64%	116	54%	

Table 2

**Documented risk of infertility discussion by gender, age and disease pre-intervention (n=260) and post intervention (n=216)**

Variable	Pre-intervention		Post-intervention		Relative Risk (95% CI)	P Value
	n / total n	%	n / total n	%		
Gender						
Males	104/153	68%	117/128	91%	1.35 (1.19-1.5)	<b>p=&lt;0.001</b>
Females	55/107	51%	77/88	88%	1.70 (1.39-2.08)	<b>p=&lt;0.001</b>
Age group						
14-19 years	72/ 121	60%	88/102	86%	1.45 (1.22-1.71)	<b>p=&lt;0.001</b>
20-25 years	87/139	63%	106/114	93%	1.48 (1.29-1.70)	<b>p=&lt;0.001</b>
Disease						
Leukaemia	35/50	70%	36/39	92%	1.32 (1.07-1.62)	<b>p=0.008</b>
Lymphoma	48/60	80%	59/63	94%	1.27 (0.99-1.63)	p=0.06
Brain cancer	12/35	34%	17/23	74%	2.15 (1.03-3.62)	<b>p=0.004</b>
Bone sarcoma	19/26	73%	26/27	96%	1.32 (1.03-1.69)	<b>p=0.03</b>
Soft tissue sarcoma	5/18	28%	13/18	72%	2.60 (1.17-5.78)	<b>p=0.02</b>
Germ cell tumour	24/37	65%	28/29	97%	1.49 (1.16-1.91)	<b>p=0.002</b>
Carcinoma	14/24	58%	12/13	92%	1.58 (1.09-2.30)	<b>p=0.02</b>
Other	2/10	20%	3/4	75%	3.75 (0.96-14.65)	p=0.06
All Patients	159/260	61%	194/216	90%	1.47 (1.12-1.63)	<b>p=&lt;0.001</b>



Table 3

**Documented referral to fertility specialist by gender, age and disease, pre-intervention (n=260) and post intervention (n=216)**

Variable	Pre-intervention		Post-intervention		Relative Risk (95% CI)	P Value
	n / total n	%	n /total n	%		
Gender						
Males	73/153	48%	88/128	69%	1.44 (1.17-1.77)	<b>p=0.0004</b>
Females	22/107	21%	33/88	38%	1.82 (1.15 -2.89)	<b>p=0.01</b>
Age group						
14-19 years	42/121	35%	50/102	49%	1.41 (1.03-1.93)	<b>p=0.03</b>
20-25 years	53/139	38%	71/114	62%	1.63 (1.27-2.11)	<b>p=0.0002</b>
Disease						
Leukaemia	20/50	40%	14/39	36%	0.90 (0.52-1.54)	p=0.69
Lymphoma	30/60	50%	42/63	67%	1.33 (0.98-1.81)	p=0.07
Brain cancer	7/35	20%	9/23	39%	1.96 (0.85-4.51)	p=0.12
Bone sarcoma	11/26	42%	21/27	78%	1.84 (1.12-3.01)	<b>p=0.015</b>
Soft tissue sarcoma	3/18	17%	7/18	39%	2.33 (0.71-7.62)	p=0.16
Germ cell tumour	17/37	46%	18/29	62%	1.35 (0.86-2.12)	p=0.19
Carcinoma	7/24	29%	9/13	69%	2.37 (1.15-4.88)	<b>p=0.019</b>
Other	0/10	-	1/4	25%	6.60 (0.32-135.38)	p=0.22
All Patients	95/260	37%	121/216	56%	1.53 (1.26-1.87)	<b>p=0.0001</b>

Table 4

**Documented outcomes of fertility preservation by gender, age and disease, pre-interventions (n=260) and post intervention (n=216)**

Variable	Pre-intervention		Post-intervention		Relative Risk (95% CI)	P Value
	n / total n	%	n /total n	%		
Gender						
Males	31/153	20%	75/128	59%	2.89 (2.05-4.09)	<b>p=&lt;0.001</b>
Females	16/107	15%	25/88	28%	1.90 (1.08-3.33)	<b>p=0.0025</b>
Age group						
14-19 years	17/121	14%	26/92	28%	2.01 (1.16-3.48)	<b>p=0.025</b>
20-25 years	30/139	22%	64/114	54%	2.60 (1.82-3.71)	<b>p=&lt;0.001</b>
Disease						
Leukaemia	10/50	20%	14/39	36%	1.43 (0.70-2.90)	p=0.32
Lymphoma	15/60	25%	34/63	54%	2.16 (1.32-3.54)	p=0.002
Brain cancer	5/35	14%	7/23	30%	2.13 (0.77-5.91)	p=0.15
Bone sarcoma	5/26	19%	16/27	59%	3.08 (1.32-7.18)	p=0.009
Soft tissue sarcoma	1/18	6%	5/18	28%	5.00 (0.66-38.65)	p=0.12
Germ cell tumour	8/37	22%	17/29	59%	2.71 (1.37-5.38)	p=0.004
Carcinoma	3/24	13%	6/13	46%	3.69 (1.10-12.39)	<b>p=0.03</b>
Other	0/10	-	1/4	25%	6.60 (0.32-135.38)	p=0.22
All Patients	47/260	18%	100/216	46%	2.56 (1.19-3.44)	<b>p=&lt;0.001</b>

Table 5.

**Post-intervention cohort, comparison of variables associated with documented fertility preservation outcomes n=216**

Variable	Documented outcome of fertility				Relative Risk* (95% CI) p value
	Yes	%	No	%	
Age group at diagnosis					
14-19	26	28%	76	72%	<b>0.50 (0.35-0.72) p=0.0002</b>
20-25	64	56%	50	44%	
Gender					
Male	75	59%	53	41%	<b>2.06 (1.44-2.96) p=0.0001</b>
Female	25	28%	63	72%	
Cancer Diagnosis					
Leukaemias	14	36%	25	64%	0.74( 0.47-1.15) p=0.18
Lymphomas	34	54%	29	46%	1.25 (0.93-1.67) p=0.13
Brain cancers	7	30%	16	70%	0.63 (0.33-1.18) p=0.16
Bone sarcomas	16	59%	11	41%	1.33 (0.94-1.89) p=0.11
Soft tissue sarcomas	5	28%	13	72%	0.52 (0.24-1.13) p=0.09
Germ cell tumours	17	59%	12	41%	1.32 (0.94-1.87) p=0.11
Carcinomas	6	46%	7	54%	0.99 (0.54-1.83) p=0.99
Other	1	25%	3	75%	0.53 (0.09-2.9) p=0.47

\*14-19 compared to 20-25 years, males compared to females, each disease compared to sum of all other diseases

**Figure Legend**

Figure 1. Documented outcomes of fertility preservation

Box 1. Interventions