Inconsistencies in fertility preservation for young people with cancer in the UK

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ABSTRACT
Objective To assess the utilisation of and funding structure for fertility preservation for children diagnosed with cancer in the UK.

Design Survey of paediatric oncologists/haematologists. Questionnaires were sent electronically with reminder notifications to non-responders.

Setting UK Paediatric Oncology Principal Treatment Centres (PTCs).

Participants Paediatric oncologists/haematologists with an interest in the effects of treatment on fertility representing the 20 PTCs across the UK.

Main outcome measures Referral practices, sources and length of funding for storage of gametes or gonadal tissue for children diagnosed with cancer in the preceding 12 months.

Results Responses were received from 18 PTCs (90%) with responses to 98.3% of questions. All centres had referred patients for fertility preservation: ovarian tissue collection/storage 100% (n=18 centres), sperm banking 100% (n=17; one centre was excluded due to the age range of their patients), testicular tissue storage 83% (n=15), mature oocyte collection 35% (n=6; one centre was excluded due to the age range of their patients). All centres with knowledge of their funding source reported sperm cryopreservation was NHS funded. Only 60% (n=9) centres reported the same for mature oocyte storage. Of the centres aware of their funding source, half reported that ovarian and testicular tissue storage was funded by charitable sources; this increased in England compared with the rest of the UK.

Conclusions Inequality exists in provision of fertility preservation for children with cancer across the UK. There is lack of formalised government funding to support international guidelines, with resultant geographical variation in care. Centralised funding of fertility preservation for children and young adults is needed alongside establishment of a national advisory panel to support all PTCs.

INTRODUCTION
The last 50 years have seen great advances in childhood cancer treatment with over 80% of patients now becoming long-term survivors.1 Long-term survivors may experience adverse late effects related to both the cancer and treatments received. Reproductive effects among survivors are well recognised, with 10–20% of long-term survivors experiencing subfertility. In a population-based study in Scotland of all women with a cancer diagnosis under the age of 40 between 1981 and 2014, cancer survivors were approximately 38% less likely to achieve pregnancy after diagnosis compared with women in the general population.2 This is a major concern for many patients and their parents at diagnosis.3 The impact of specific chemotheraphy and radiation treatment regimens on fertility is increasingly understood.4–7 Given the risks to fertility from cancer and cancer treatments, strategies to preserve fertility have been developed.8 Evidence-based recommendations regarding fertility preservation for children, adolescents and young adults with cancer, developed by the PanCar-E.LIFE consortium and the International Late
Effects of Childhood Cancer Guideline Harmonisation Group, have been produced. Several countries have published their own guidance on fertility preservation including the American Society of Clinical Oncology (ASCO), Children’s Cancer and Leukaemia Group, Children’s Oncology Group and the British Fertility Society (BFS).

Within the UK, paediatric cancer services are delivered through 20 specialist Principal Treatment Centres (PTCs). Current specialist clinical guidelines recommend that ovarian tissue cryopreservation is offered to girls with cancer at risk of subfertility and premature ovarian insufficiency, while testicular tissue cryopreservation may be offered to boys at high risk of gonadotoxicity, although this remains experimental.

There is an absence of standardised National Health Service (NHS) commissioned and funded fertility preservation services for children with cancer across the UK. Funding of fertility preservation for prepubertal individuals is anecdotal and no official policy exists to guide practice. The NHS-funded storage varies according to different commissioning bodies, such as individual Clinical Commissioning Groups (CCGs), with the duration of storage limited to 10 years in some areas. In postpubertal girls, storage of oocytes, embryos or ovarian tissue may be appropriate, with indefinite NHS funding available for the first two of these options.

In the absence of central NHS funding arrangements, there is the potential for inequality and significant variation in service provision across the UK for young people with cancer who may be at risk of future long-term subfertility. To understand the exact situation across the UK and to inform delivery of equitable and optimal future services, we aimed to explore current service provision and funding structures for fertility preservation in patients diagnosed with childhood cancer (<18 years of age) across the UK.

METHODS
Study design
This was a cross-sectional electronic survey of all 20 PTCs across the UK. A clinician with a specialist interest in cancer after-care (and, where available, primarily in reproductive late effects) was identified at each centre and invited via email to participate. The invited participant was asked to answer on behalf of their institution and advised to contact the researchers if another clinician was identified as more appropriate to answer on behalf of that institution. Reminder emails were sent twice to non-responders.

Survey questions
Participants were asked a total of 10 questions with regard to both male and female patients, with distinction between pre- and postpubertal patients. The study opened in July 2019 and closed in August 2019. Questions covered referral practices over the preceding 12 months and included sources of funding, length of time funding is available for storage of gametes or gonadal tissue and estimated numbers of referrals. Referral numbers were collected in ranges (0, 1–5, 6–10, 11–15, 16–20, 21–25, 26–50, 51–75, 76–100 and >100) rather than discrete numbers in the interest of simplification for the participant. An estimation was deemed preferable over an omitted response as it was unlikely exact data would be readily available to participants. Questions were designed to be closed, with limited space for free text in order to facilitate analysis (online supplemental file 1).

Data analysis
Descriptive statistics were used to analyse the data. The results are reported predominantly as individual responses as a proportion of the whole to show variation across the UK. Where reporting of individual results had the potential for centres to be identified, responses were collated into four geographical groupings to protect anonymity of individual PTCs. One responding PTC does not routinely care for new patients above 13 years of age. Their data were therefore excluded from analysis with regard to questions relating to mature oocyte or sperm storage.

Ethical approval
The research was approved by the University of Leeds School of Medicine Research Ethics Committee on 30 May 2019 (study reference MREC18-019).

RESULTS
Eighteen of 20 (90%) PTCs responded with good geographical representation across the UK. Responding PTCs were assigned to one of four groups on the basis of geographical area (figure 1). Data completeness was high, with 98.3% of questions answered. The questionnaire was composed of 10 stem questions and 30 questions in total. Nine individual questions were unanswered out of the 540 (30 questions for 18 centres) questions in total. All submitted responses were valid and included in the analysis.

Refrerrals of patients aged <18 years for fertility preservation
All PTCs had referred patients for fertility preservation in the preceding 12 months (table 1). Within this time period, responding PTCs collectively estimated that 479 individual referrals for fertility preservation had been made with an estimated range of 338–620 cases (table 2). The majority of these referrals were for postpubertal boys.

Girls
Centres reported 95 (range 61–130) estimated referrals for prepubertal girls and 82 (range 55–110) for postpubertal girls. All centres had referred at least one case for ovarian tissue cryopreservation (collection and storage): 18/18 (100%). Fewer centres recorded at least one referral for mature oocyte storage: 6/17 (35%).

Boys
Centres reported 83 (range 51–115) estimated referrals for prepubertal boys and 218 (range 171–265) estimated referrals for postpubertal boys. Each centre had referred at least one case for sperm cryopreservation (17/17 (100%)) and 15/18 (83%) centres had also referred at least one boy for testicular tissue cryopreservation (The PTC that does not treat newly diagnosed patients older than 13 years was excluded from sperm cryopreservation reporting).
Geographical variation

Most variation by geographical region was seen for mature oocyte storage and testicular tissue storage. With regard to mature oocyte storage, 0% of centres in the Midlands and East of England, 25% in the South of England, 50% in the North of England and 60% of centres located in the Devolved Nations had referred at least one patient while, for testicular tissue storage, 75% of centres in the North of England, 80% in the South of England and Devolved Nations, and 100% of centres in the Midlands and East of England had referred one or more patients.

Funding sources

Wide variation was reported in funding sources by available fertility preservation technique (figure 2A,B). In several cases the participants reported being unaware of the funding source: 2/17 (12%) for both mature oocyte and sperm storage, 2/18 (11%) for ovarian tissue cryopreservation and 3/18 (17%) for testicular tissue cryopreservation. Of the centres who were aware of their regional funding source, half reported that ovarian and testicular tissue storage was funded by charitable sources.

Girls

Nationally, for centres reporting their funding source, mature oocyte storage was reported as health service funded (via CCGs, local commissioning groups, NHS or Health boards) in 9/15 (60%) centres, contrasting with 3/16 (19%) centres reporting health service regulated funding arrangements for ovarian tissue cryopreservation.

Boys

Sperm cryopreservation was reported as being NHS funded by all responding PTCs who were aware of the funding source (15/15 (100%)). A few participating centres reported the receipt of health service funding for testicular tissue storage (2/15 (13%)).

Table 1

<table>
<thead>
<tr>
<th>Geographical area (n=number of centres in group)</th>
<th>Fertility preservation technique</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sperm collection and storage (% responding centres)</td>
<td>Testicular tissue collection and storage (% responding centres)</td>
<td>Mature oocyte collection and storage (% responding centres)</td>
<td>Ovarian tissue collection and storage (% responding centres)</td>
</tr>
<tr>
<td>UK (n=18)</td>
<td>17 (100)</td>
<td>15 (83)</td>
<td>6 (35)</td>
<td>18 (100)</td>
</tr>
<tr>
<td>Devolved Nations (n=5)</td>
<td>5 (100)</td>
<td>4 (80)</td>
<td>3 (60)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Midlands and East of England (n=4)</td>
<td>4 (100)</td>
<td>4 (100)</td>
<td>0 (0)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>North of England (n=4)</td>
<td>4 (100)</td>
<td>3 (75)</td>
<td>2 (50)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>South of England (n=4/5)*</td>
<td>4/4 (100)</td>
<td>4/5 (80)</td>
<td>1/4 (25)</td>
<td>5/5 (100)</td>
</tr>
</tbody>
</table>

*One centre was excluded for sperm and mature oocyte storage due to difference in upper age limit (13 years) of patients treated compared with other centres.
Geographical variation in funding source

Geographical variation was seen with regard to funding sources for both ovarian and testicular tissue cryopreservation. Centres located in the Devolved Nations reported no reliance on charitable sources for funding, instead reporting either health service commissioned funding, funding via research or publicly funded health service sources on a case-by-case basis. This was in contrast to centres located in England which, when aware of their funding sources, collectively reported a heavy reliance on charitable sources: 3/4 (75%) in the Midlands and East of England, 2/2 (100%) in North of England and 4/4 (100%) in South of England.

Duration of funded storage

Variation was reported in the length of time funding was available for each technique across the UK. However, the majority of respondents were uncertain of the length of funding available at the time

Table 2  Principal Treatment Centre (PTC) estimated number of referrals by age over a 12-month period

<table>
<thead>
<tr>
<th>Region</th>
<th>Boys, postpubertal</th>
<th>Boys, prepubertal</th>
<th>Girls, postpubertal</th>
<th>Girls, prepubertal</th>
<th>All &lt;18-year-olds</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>171–265 (218)</td>
<td>51–115 (83)</td>
<td>55–110 (82)</td>
<td>61–130 (95)</td>
<td>338–620 (429)</td>
</tr>
<tr>
<td>Scotland, Wales and Northern Ireland (Devolved Nations)</td>
<td>15–25 (20)</td>
<td>5–25 (15)</td>
<td>5–25 (15)</td>
<td>10–30 (20)</td>
<td>35–105 (70)</td>
</tr>
<tr>
<td>Midlands and East of England</td>
<td>14–30 (22)</td>
<td>14–30 (22)</td>
<td>13–20 (17)</td>
<td>14–30 (22)</td>
<td>55–80 (68)</td>
</tr>
<tr>
<td>North of England</td>
<td>59–95 (77)</td>
<td>18–30 (24)</td>
<td>29–45 (37)</td>
<td>18–35 (26)</td>
<td>124–205 (165)</td>
</tr>
<tr>
<td>South of England</td>
<td>83–115 (99)</td>
<td>14–30 (22)</td>
<td>8–20 (14)</td>
<td>19–35 (27)</td>
<td>124–200 (162)</td>
</tr>
</tbody>
</table>

Participants were asked to provide an estimate of their centre’s number of referrals using the following predefined ranges: 0, 1–5, 6–10, 11–15, 16–20, 21–25, 26–50, 51–75, 76–100, >100.

Figure 2a Source of funding for fertility preservation of gametes or tissue across the United Kingdom for female patients

*CGG = clinical commission groups
**CCG = local commissioning groups
***NHS = National Health Service

Figure 2b Source of funding for fertility preservation of gametes or tissue across the United Kingdom for male patients

*CGG = clinical commission groups
**CCG = local commissioning groups
***NHS = National Health Service

Figure 2  Source of funding for fertility preservation of gametes or tissue across the UK for (A) girls and (B) boys.
of storage (≥50% for each technique). Hence, it is not possible to provide detailed evaluation other than to demonstrate the wide range of responses from <5 years to indefinite. Respondents were more likely to indicate that ovarian and testicular tissue storage had indefinite funding while time limitations on sperm and oocyte storage existed.

Management following termination of routinely funded storage period
The PTCs were asked for their unit’s usual first step in management for a patient when the agreed funding plan for the stored gametes/tissue had run out. Scenarios explored included patients whose fertility (a) appeared unaffected after their treatment, (b) had been possibly affected (eg, changes in one or more semen parameters outside of the normal range) or (c) was severely affected (eg, azoospermia). For each scenario the respondent was instructed to assume that the patient wished to continue with the storage of the gametes or tissue. Over 50% reported no experience of the scenarios; however, for those who did have experience, significant variation in practice was identified (figure 3).

DISCUSSION
To the best of our knowledge, this is the first national evaluation of fertility preservation activity for young people with cancer which includes boys and girls as well as funding sources. It was performed because of concerns among professional groups of inequalities across the UK in the provision of support for young people facing cancer treatment and the potentially associated subfertility. All centres referred patients for fertility preservation, although marked variation in both services offered and funding sources across the UK have been identified. Charitable funding was used in 50% of centres for ovarian and testicular tissue storage while health service (NHS) funding was available in all PTCs for sperm cryopreservation.

Through knowledge of cancer incidence rates and activity levels at PTCs across the UK, we estimate that approximately 25% of patients were offered fertility preservation. While the data identify that referral for fertility preservation was offered in all children’s cancer centres (PTCs), it is not known whether it was offered to all eligible patients as a single referral over the 12-month period would lead to a positive indication of service utilisation. Knowledge of funding was not universal among respondents; reproductive medicine units were not invited to participate and potentially the data could have been enriched with their complementary responses and knowledge of funding sources and duration.

NHS funding was reported to be available for sperm banking, the most established fertility preservation technique, in 100% of PTCs. This is unsurprising given its long-standing history of clinical success and relative ease of collection and storage. The equivalent practice in girls for storage of gametes is mature oocyte storage. While having a long-established clinical evidence base of success,18 this procedure does not appear to have the same availability of health service funding with only 60% of centres with knowledge of funding pathways reporting health service commissioned NHS funding.

Of the almost 500 cases estimated to have been referred to undergo some form of fertility preservation technique over the 12-month period, approximately 20% are reported to be reliant on charitably-sourced funding, most markedly in England compared with the other nations of the UK. The reliance on charitable sources, particularly for ovarian and testicular tissue cryopreservation, may lead to restrictions in access. Patients may be disadvantaged in the future without robust centralised funding, with the presented data identifying that service users in England may be more susceptible to this than residents of the Devolved Nations of the UK.

The majority of consultant paediatric oncologists/haematologists responding to the survey were unaware of the duration of funding for all the available fertility preservation options undertaken at their centre. Given the variability in funding sources and often time-limited nature of the funded provision, this lack of knowledge needs to be addressed to ensure patients receive accurate counselling and are provided with the most appropriate options for ongoing storage after the duration of NHS, or other source of funding expires.

While it is beyond the scope of this paper to explore exactly why these differences exist, it is essential that they are resolved.

Figure 3 First step in management of a patient where agreed funding has expired but the individual wishes to continue to store their gametes or tissue. *Individual funding request: on an individual basis, there may be situations where a clinician believes that their patient’s clinical situation is so different from other patients with the same condition that they should have their treatment paid for when other patients would not. In such cases, NHS clinicians can ask NHS England, on behalf of a patient, to fund a treatment which would not usually be provided by NHS England for that patient. This request is called an Individual Funding Request (IFR) in England, an Individual Patient Treatment Request (IPTR) in Scotland, an Individual Patient Treatment Request elsewhere.
A combination of differing awareness of, and reliance on, NHS versus charitable funding and varying departmental practices may underpin some of these differences, and further research into the reasons for these differences is necessary alongside strategies to improve equity of access to fertility preservation.

CONCLUSION
Maintenance of adult life choices is a key marker of successful outcomes from childhood cancer and retained fertility is rated as a major priority by survivors of childhood cancer and their families.\(^2\) While it is reassuring that so many cases are being offered fertility preservation across the UK, urgent action is required to ensure that NHS funding is available for all to provide the appropriate security preservation across the UK, urgent action is required to ensure that While it is reassuring that so many cases are being offered fertility support all PTCs to provide optimal care with the elimination of any recognised best practice. To support equity of access, we recommend (1) centralised funding of fertility preservation strategies mandated by current quality standards for each developed health nation and (2) establishment of a national multidisciplinary team available to support all PTCs to provide optimal care with the elimination of any geographical disadvantage related to place of care.

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The idea for this study came from AG, CMH and HLN. The survey was designed by HLN, with input from AG, CMH, HMP and AIF-MB, RC, VG, MK-W, SL, RTM, RS, WHS and DY assisted with data collection and analysis. All authors contributed to the final manuscript and have approved it for publication.

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Supplemental material
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