

SURVEILLANCE FOR WILMS TUMOUR IN AT-RISK INDIVIDUALS – PRAGMATIC RECOMMENDATIONS FOR BEST PRACTICE

The Wilms Tumour Surveillance Working Group

April 2005

SUMMARY OF RECOMMENDATIONS

- **Surveillance should be offered to children at >5% risk of Wilms tumour [D].**
- **Surveillance should only be offered after review by a Clinical Geneticist [D].**
- **Surveillance should be by renal ultrasonography every 3-4 months [D].**
- **Surveillance should continue until 5 years in all conditions except Beckwith-Wiedemann syndrome, Simpson-Golabi-Behmel syndrome and some Familial Wilms pedigrees where it should continue until 7 years [D].**
- **Surveillance can be undertaken at a local centre but should be performed by someone with experience of paediatric ultrasonography [D].**
- **Screen-detected lesions should be managed at a specialist centre [D].**

The grading scheme for the recommendations [A, B, C, D] is described in Appendix 1. The evidence on which the guidance is based is outlined below.

INTRODUCTION

Wilms tumour (WT) is an embryonal tumour of the kidney that affects 1 in 10,000 children and is diagnosed in ~80 children in the UK each year. Treatment for Wilms tumour is one of the foremost successes of paediatric oncology, with long-term survival over 90% for localised disease and over 70% for metastatic disease. Most tumours occur in otherwise well children, but a small number occur in children with genetic syndromes. Regular surveillance in children thought to be at increased risk of WT has become widespread in the UK, USA and parts of Europe. However, the potential risks and benefits of surveillance are finely balanced and there is no clear evidence that screening reduces mortality or morbidity. Moreover, no guidance as to how WT surveillance should be implemented has been available. This has resulted in ad-hoc surveillance protocols lacking in consistency of practice and/or equity of provision. In turn this has led to confusion, controversy and dissatisfaction for patients and clinicians. The rarity of WT associated conditions effectively precludes an appropriately powered, prospective, randomised study to evaluate efficacy of WT surveillance, and it is very unlikely that evidence-based guidelines to inform the implementation of Wilms tumour screening will become available.

In 2004, we formed a working group of Clinical Geneticists (EM, NR, LW), Paediatricians (AC), Paediatric Oncologists (KPJ, GL) and Radiologists (IK, CO, OO) to produce guidelines for WT surveillance, based on a review of current practice and available evidence, as outlined below.

BACKGROUND

Wilms tumour treatment results in long-term survival in most children

WT treatment is determined by stage and risk classification of the tumour (Appendix 2). Substantial progress has been made over the last few decades and long-term survival for localised disease (stage 1-3) is now greater than 90%, and for metastatic disease (stage 4) is over 70% (Pritchard-Jones, 2002). Surgery, chemotherapy and radiotherapy are utilised to treat WT, but there are important differences in how these modalities are used across the world. In the USA, immediate nephrectomy is the recommended approach and the intensity of subsequent chemotherapy and the need for radiotherapy is determined by the stage of the chemo-naïve tumour and its histology. In the UK and Europe, pre-operative chemotherapy to 'down-stage' tumours is given prior to delayed nephrectomy. These differing management strategies result in 30% of American patients with localised tumours having stage 3 disease compared with 15% of such patients from the UK and Europe (Pritchard-Jones, 2002, Kalapurakal et al. 2004).

Currently in the UK, 45% of WT cases receive only Vincristine and Actinomycin D. 55% of cases receive doxorubicin and additional drugs (cyclophosphamide, carboplatin and etoposide) are given to high risk stage 2/3 and stage 4 cases that respond poorly to initial chemotherapy. Approximately 30% of cases also receive irradiation. Clinical trials of different treatment regimens are ongoing and treatment may alter as a result of these, or future, studies.

With improving survival, efforts to reduce treatment-related morbidity have become increasingly important. Vincristine, Actinomycin D and surgery are generally well tolerated with low risks of long-term side effects. Anthracyclines are associated with long-term cardiotoxicity and cyclophosphamide, carboplatin and etoposide are also associated with significant side-effects (Pein F et al. 2004; Oeffinger and Hudson, 2004). Radiotherapy can result in adverse effects including localised skin damage, reproductive problems and second malignancy. (Hawkins et al. 1989; Jenkinson et al. 2004). Thus, interventions that reduce disease stage such that radiotherapy and/or more toxic chemotherapies are not required may reduce treatment-related morbidity.

Several genetic conditions predispose to Wilms tumour

The causes of WT are unclear, but genetic factors are strongly implicated. This comes partly from the observation that WT incidence is subject to ethnic variation (Stiller, 2004), and partly because several genetic conditions associated with WT are known. Many case reports of WT occurring in children with a large number of different conditions have been published. However, for many of these conditions there is no proven association with WT and very few conditions are associated with risks of WT greater than 5%. These are outlined below and in Table 1.

WT1 associated syndromes. WT1 is a transcription factor located on chromosome 11p13. Abrogation of WT1 function has been associated with a variety of phenotypes. Three major WT1 conditions are recognised, WAGR syndrome, Denys-Drash syndrome and Frasier syndrome.

WAGR syndrome (**W**ilms-**a**niridia-**g**enital malformations-**m**ental **r**etardation) is caused by a microdeletion at 11p13 that deletes both WT1 and PAX6, and results in aniridia in all cases. The condition is variably associated with Wilms tumour, genitourinary malformations, mental retardation and a variety of other conditions such as congenital heart disease (Crolla et al. 1997). The estimated risk of WT is at least 50% (Narahara et al. 1984).

Denys-Drash syndrome is caused by intragenic *WT1* mutations, typically missense alterations of the zinc-finger domains in exons 8 and 9. Classically, the condition includes the triad of WT, genitourinary malformations and nephropathy but various combinations of these features have been reported, and children with just one of the three cardinal features and a pathogenic *WT1* mutation are well recognised (Little and Wells, 1997; Schumacher et al. 1998; Little et al. 2004; Royer-Pokora et al. 2004). The risk of WT is not precisely known, but is clearly high (at least 50%).

Frasier syndrome describes the association of gonadal dysgenesis often resulting in sex reversal in males, progressive nephropathy and gonadoblastoma. It is caused by *WT1* splicing mutations in intron 9 that alter the ratio of *WT1* isoforms. Only 4 of 48 (8%) published cases have developed WT (Coppes et al. 1993; Barbosa et al 1999; Loirat et al 2003).

Familial Wilms Tumour. Only 1-3% of Wilms tumour cases cluster within families. Rarely, families have *WT1* mutations (2 of 40 families in our series, Rahman, unpublished data). Males in *WT1* families usually have urogenital abnormalities, but these may be very mild. Two familial Wilms tumour genes have been mapped, *FWT1* on chromosome 17q21 (Rahman et al. 1996) and *FWT2* on chromosome 19q13 (McDonald et al. 1998), but neither gene has been identified. There are families unlinked to any of the known loci, indicating that other familial Wilms tumour genes exist (Rapley et al. 2000). There is marked inter- and intra-familial variability with respect to penetrance, age-of-onset, stage and pathology of tumours. The risk of WT is very variable but estimated to be at least 30% overall (Rahman, unpublished data).

Fanconi anemia D1 (biallelic *BRCA2* mutations). Fanconi anemia is a rare autosomal recessive condition characterised by variable congenital abnormalities, short stature, bone marrow failure, hypersensitivity to DNA crosslinking agents and a predisposition to haematological malignancies. The condition is heterogeneous with nine predisposition genes identified (Tischkowitz and Hodgson, 2003). Only one subgroup, D1, has an increased risk of WT. Fanconi anemia-D1 is due to biallelic *BRCA2* mutations and 5 of 23 reported cases have developed WT (Reid et al. 2005). Identification is important, as affected cases are exquisitely sensitive to DNA damaging chemotherapies, and radiotherapy may increase the risk of subsequent cancers. Monoallelic (i.e. heterozygous) *BRCA2* carriers are at elevated risk of breast and ovarian cancer but not childhood cancer (Reid et al. 2005).

Mosaic Variegated Aneuploidy (biallelic *BUB1B* mutations). Mosaic variegated aneuploidy is a rare autosomal recessive condition characterised by mosaic aneuploidy, mostly monosomies and trisomies, involving multiple different chromosomes and tissues. Affected individuals are usually growth retarded with microcephaly and can have a variety of additional features. Biallelic *BUB1B* mutations appear to cause most cases and are associated with WT risk >20% (Hanks et al. 2004).

Beckwith-Wiedemann syndrome. This is the commonest WT-associated condition, affecting 1 in 13,000 children. It is an imprinting disorder characterised by overgrowth, macroglossia, and abdominal wall defects. Additional features include hemihypertrophy, neonatal hypoglycaemia and urogenital abnormalities. Beckwith-Wiedemann syndrome is caused by dysregulation of imprinted genes on chromosome 11p15 and there are multiple mechanisms by which this can occur (Maher and Reik 2000; Weksberg et al. 2003). The overall risk of embryonal tumours, most of which are WT, is estimated at 5-10% (Wiedemann HR, 1983).

There is increasing evidence that WT risk varies for different causes of Beckwith-Wiedemann syndrome (Engel et al. 2000; Bliiek et al. 2001; DeBaun et al. 2002; Bliiek et al. 2004, Maher, personal communication). Approximately 50% of cases are associated with loss of methylation of KvDMR1 at imprinting centre 2 but none of these have developed WT. Similarly, no case with a mutation of *CDKN1C*, (which account for ~40% of familial cases) has developed WT. Conversely, WT does occur in cases with uniparental disomy (UPD) 11p15, cases with defects at imprinting centre 1 affecting *H19* expression, and in cases that fulfil the diagnostic criteria for Beckwith-Wiedemann syndrome but in which no specific underlying cause can be found (Bliiek et al. 2004; Rahman, 2005).

Simpson-Golabi-Behmel syndrome. This is a rare X-linked disorder due to *GPC3* mutations and partial gene deletions. Affected males are usually very tall with distinctive facies. Simpson-Golabi-Behmel syndrome is associated with congenital heart defects, skeletal and urogenital anomalies, but intelligence is usually normal. There is a risk of embryonal tumours, most of which are WT, estimated at ~10% (Mariani et al. 2003). Carrier females are not at increased risk of WT.

Perlman syndrome. This is a very rare autosomal recessive condition associated with high risks of WT in addition to macrosomia, nephromegaly, cryptorchidism, neonatal hypoglycaemia and facial dysmorphism (Henneveld et al. 1999). The cause is unknown, although in one case a *GPC3* mutation was identified (Li et al. 2001).

Hemihypertrophy. Isolated hemihypertrophy (also known as hemihyperplasia) is a poorly defined entity. The term is inconsistently used in cases with various forms of asymmetric growth. There is uncertainty about which regions of the body can be involved and the degree / extent of asymmetry required to make the diagnosis. One study has evaluated the risk of embryonal tumours in isolated hemihypertrophy with 6 of 168 (3.5%) cases developing WT (Hoyme et al. 1998). It has been proposed by some that hemihypertrophy is a 'forme fruste' of Beckwith-Wiedemann syndrome. Occasional hemihypertrophy cases with uniparental disomy 11p15 have been reported, though these were above the 97th centile for growth (Grundy et al, 1991; West et al, 2003) and many hemihypertrophy cases without uniparental disomy 11p15 are known.

The efficacy of Wilms Tumour surveillance is unclear

The identification of WT susceptibility syndromes led to the proposition that asymptomatic children 'at-risk' of WT would benefit from cancer surveillance. Over the past few decades screening for WT has become routine in many countries although its efficacy has not been formally demonstrated.

The efficacy of a surveillance procedure can be evaluated in a number of ways the most simple of which is crude survival (Prorok, 1992). For conditions such as Wilms tumour where survival rates are very high, it is unlikely that screening will lead to a substantial decrease in mortality. An alternative, or additional, basis on which to evaluate screening could be a more favourable stage distribution among screened patients resulting in lower treatment-related morbidity.

To date, three retrospective evaluations of WT screening have been published (Green et al. 1993; Craft et al. 1995; Choyke et al 1999). In a small UK Study of 41 children with WT and either aniridia, Beckwith-Wiedemann syndrome or hemihypertrophy, there was no difference in outcome or stage distribution of screened and unscreened cases (Craft et al. 1995). By contrast, a small American study reported a significant difference in stage distribution between screened and unscreened individuals. This study compared the frequency

of late-stage (3 or 4) WT diagnosed in screened Beckwith-Wiedemann syndrome cases to that in unscreened patients with either Beckwith-Wiedemann syndrome or hemihypertrophy. None of 12 children whose WT were identified by screening had late-stage disease compared with 42% of the unscreened cases (Choyke et al. 1999). It is noteworthy that all screened cases in this study had Beckwith-Wiedemann syndrome, whereas the majority of unscreened cases had hemihypertrophy. There was no difference in the stage distribution between the screened and unscreened Beckwith-Wiedemann syndrome cases, raising the possibility that differences in the natural history of tumours in different conditions may have been a factor. Overall, there is currently no definitive evidence that screening results in a significant decrease in either overall mortality or tumour stage.

In evaluating any screening test it is important to consider the potential negative sequelae, for example a false positive result. In the study by Choyke et al, three of 15 screened individuals had false positive scans. Two children were found to have renal cysts after extensive further imaging and major surgery, with one child having a radical nephroureterectomy. The third child also had a kidney removed, which showed nephroblastosis but no Wilms tumour (Choyke et al. 1999). These cases highlight the potential difficulties in interpretation of screening ultrasounds in individuals with conditions that are associated with cystic and/or nodular changes in the kidney. Additionally, although difficult to quantify, the anxiety and practical difficulties associated with regular surveillance should not be underestimated.

A randomised study to evaluate WT surveillance is not justifiable

The available evidence suggests the benefits of screening may be limited and the potential risks appreciable. Ideally, a prospective, randomised study of screening against no screening to evaluate the utility of WT surveillance is required, and has been advocated by several authors (Green et al. 1993; DeBaun et al. 1996; Choyke et al. 1999). However, there are considerable obstacles to the success of such a study. Conditions with high risks of WT are rare and therefore an international multi-centre study conducted over many years would be required to effectively evaluate screening. This would be complex and very expensive to conduct. Moreover, there are considerable uncertainties about the WT risks and natural history of WT in different conditions, and even different sub-types of conditions, and changes in WT treatment or staging over the course of the study could confound the results. These difficulties and uncertainties may lead to the study giving inconclusive results even after many years.

Wilms tumour surveillance probably detects tumours at lower stage

It is difficult to justify the expense of a randomised study of WT screening, particularly when a definite outcome is not guaranteed. However, neither is it acceptable to withdraw screening simply because the rarity of at-risk conditions precludes formal evaluation of efficacy. Moreover, as the accepted practice is to screen children considered at-risk, it is unlikely that a recommendation to withdraw screening simply because one cannot definitively prove it is of benefit would be adhered to.

Tumours detected by WT surveillance should, overall, be smaller than tumours that present clinically as they will have been detected earlier. There is evidence to support this from Germany, where 10% of WTs are diagnosed prior to symptoms. Moreover, in Germany, asymptomatic tumours are overall of lower stage than tumours that present due to clinical symptoms (Graf, personal communication). As lower-stage tumours currently receive less therapy, screening could plausibly result in lower mortality and/or a reduction of treatment-related morbidity in some children. We believe it is reasonable to offer surveillance on this premise to children at increased risk of Wilms tumour.

RECOMMENDATIONS

Surveillance should be offered to children at >5% risk of Wilms tumour

Given the finely balanced potential positive and negative sequelae of WT screening, only conditions in which a clearly increased risk of WT should be offered screening. We have arbitrarily set the threshold at 5%, although the majority of cited conditions are associated with risks greatly in excess of this (Table 1). Some conditions are associated with increased risks of other tumours but screening and management of these are beyond the scope of this document and are not discussed. UK laboratories offering the cited molecular tests are given in Appendix 3.

Table 1. Molecular and phenotypic abnormalities with Wilms Tumour risk in excess of 5%.

Gene	Phenotypes	Tests available	Who should have WT surveillance
WT1	WAGR Aniridia Denys-Drash Frasier Isolated WT Familial WT Isolated nephropathy	Karyotype 11p13 FISH Mutation screen	All
FWT1/FWT2/ Other genes	Familial WT	No	All potential carriers
BRCA2 (biallelic)	Fanconi anemia Some childhood cancer clusters	Mutation screen	All
BUB1B	Mosaic variegated aneuploidy	Mutation screen (research)	All
11p15 defects	Beckwith-Wiedemann Some hemihypertrophy cases	Karyotype KvDMR1 methylation, 11p15 uniparental disomy CDKN1C (research)	Not KvDMR1 Not CDKN1C All others
GPC3	Simpson-Golabi-Behmel Some Perlman cases	Mutation screen	All
Unknown	Perlman	None	All

WT1 associated syndromes. All children with aniridia should have a constitutional karyotype and FISH using probes for both *PAX6* and *WT1*, whether or not any additional features of WAGR are present. If *WT1* is deleted, the risk of WT is high and surveillance should be offered. If *WT1* is not deleted the WT risk is similar to the population risk, and no screening or renal follow-up is required, either for the proband or relatives.

Any child with either a truncating *WT1* mutation or a missense mutation in the zinc finger domains is at substantial risk of WT (Little and Wells, 1997). Many children will already have WT when the *WT1* mutation is identified and will already be under follow-up. Most mutations occur *de novo* in which case there is a potential offspring risk but other relatives will not be at risk. Mutation testing in parents and, if appropriate, other relatives can be undertaken and screening offered to mutation-positive cases. Care must be exercised in the interpretation of missense alterations outside zinc finger domains. These should be considered unclassified variants unless shown to be *de novo* and should not be used as a basis for predictive testing or screening unless there is clear evidence of pathogenicity.

WT1 splicing mutations in intron 9 that alter the ratio of *WT1* isoforms are associated with risks of WT ~8% and are therefore eligible for surveillance.

Familial Wilms Tumour. A small proportion of familial clusters are due to *WT1* mutations. *WT1* mutation-positive cases should be offered surveillance and predictive testing would be available for relatives. Testing is currently not available for *FWT1* or *FWT2*, as neither gene has been identified, but NR would be keen to include any family in on-going research to identify familial WT genes. At-risk individuals in families with more than one Wilms tumour case should be offered surveillance. Rare familial clusters of WT and neuroblastoma are known and at-risk individuals from such pedigrees would also be eligible for surveillance. Non-syndromic familial clusters of other childhood cancers and WT are not associated with risks of WT >5%.

Fanconi anaemia D1. Biallelic *BRCA2* mutation carriers should be offered surveillance. Monoallelic (i.e. heterozygous) *BRCA2* carriers are at elevated risk of breast and ovarian cancer but not childhood cancer and do not require WT surveillance.

Mosaic Variegated Aneuploidy. Cases with either cytogenetic confirmation of the diagnosis and/or demonstrated biallelic *BUB1B* mutations should be offered surveillance.

Beckwith-Wiedemann Syndrome. It has been suggested that only Beckwith-Wiedemann syndrome cases with nephromegaly are at-risk of WT, but this was based on a single small study that has not been substantiated (DeBaun et al. 1998). Moreover, in Beckwith-Wiedemann syndrome cases with hemihypertrophy, WT is equally likely to occur in the kidney on the non-overgrown side (Green et al. 1993). Thus, at the current time, kidney size is not a robust indicator of cancer risk and should not be used to stratify cases.

Diagnostic testing for methylation status at KvDMR1 and for UPD 11p15 is currently available. *CDKN1C* mutation testing may be available on a research basis in familial cases. Beckwith-Wiedemann syndrome cases with loss of methylation at KvDMR1 or *CDKN1C* mutations do not require WT surveillance, as current evidence suggests the risk is much lower than 5%. All other cases should be offered surveillance, including cases that fulfil the diagnostic criteria for Beckwith-Wiedemann syndrome but in whom no molecular cause is identified.

Simpson-Golabi-Behmel syndrome. Affected males with *GPC3* mutations or deletions should be offered surveillance. Carrier females are not at increased risk of WT. The WT risk of *GPC3*-negative cases is not known but is not >5% overall. Such cases are likely to be highly heterogeneous in origin and should not be referred for surveillance.

Perlman syndrome. The cause of this condition is unknown, although in one case a *GPC3* mutation was identified and mutation testing should be considered in males (Li et al. 2001). Early morbidity and mortality is high and thus most affected cases are already under close supervision. Unaffected siblings and extended relatives do not require surveillance.

Hemihypertrophy with 11p15 defects. The utility of hemihypertrophy as a surrogate indicator of WT risk is questionable. Data from both USA and UK demonstrated that in ~50% of hemihypertrophy cases with cancer the asymmetry was only detected at cancer presentation or later (Green et al. 1993; Craft et al 1995). Nevertheless, WT screening in children with asymmetric growth is widespread and such cases now constitute the largest group undergoing surveillance in the UK. The WT risk overall has been estimated at only 3.5% (Hoyme et al.

1998). A small proportion of asymmetric children have uniparental disomy 11p15. Their WT risk is similar to Beckwith-Wiedemann syndrome cases with uniparental disomy 11p15 and is >5%. We recommend that WT surveillance should be offered to hemihypertrophy cases with uniparental disomy 11p15 but not to other cases with asymmetric growth. We (NR) are starting a three-year study to clarify the clinical and cancer phenotypes associated with hemihypertrophy and to identify the underlying causes. Any asymmetric growth case will be eligible for the study and all will be screened for 11p15 defects and hence those at increased WT risk will be identifiable. It is hoped that these, or other studies, will identify clearly definable subgroups of children with asymmetric growth that have risks of WT >5%, who would be eligible for surveillance.

Children should only be referred for screening after review by a Geneticist

For the conditions discussed above, diagnostic molecular tests are available that directly impact on eligibility for surveillance and that have genetic implications for cases and their families. We therefore recommend that a Clinical Geneticist reviews all children in whom the above diagnoses are being considered. The Geneticist can undertake the appropriate tests, discuss the benefits and risks of surveillance and refer the child for screening, if appropriate.

Renal ultrasonography is the optimal screening modality

Abdominal ultrasound is the best screening modality currently available. It is readily accessible, non-invasive and has minor resource implications. Abdominal palpation has been proposed as an alternative, but cannot detect very small tumours and is therefore unlikely to provide appreciable benefit compared with no screening. Magnetic resonance imaging (MRI) or computed tomography (CT) scanning may be sensitive in detecting small lesions, but these modalities are unacceptable as many children would require sedation and CT carries a significant radiation burden. Moreover, CT and MRI are not as readily available and would have substantial resource implications.

The sensitivity of renal ultrasonography in children is not certain and may be influenced by the equipment used, machine settings and operator skills. Extrapolating from adult data the sensitivity is estimated to be 73-89% and the specificity 85-97% (Schmidt et al. 2003). Screening ultrasounds can be undertaken at the local hospital but should be performed by a radiologist or sonographer with experience of paediatric ultrasonography. Recommendations for operational procedures are given in Table 2.

Table 2. Suggested procedure for renal sonography in children at-risk of WT.

Equipment	High-resolution probes and paediatric settings. Linear 7-10 MHz in infants, curvilinear 6-8 MHz probe in toddlers.
Preparation	Fasting and bladder preparation are not required.
Target organ	Kidneys only.
Technique	Appropriate focal point and time gain settings. The whole renal parenchyma should be imaged longitudinally and transversely with the child both supine and prone.
Normal variants	Dromedary hump, column of Bertin, duplex or bifid collecting system(s).
Suspicious lesions	Solitary or multiple cystic or solid parenchymal lesions with or without sonographical signs of expansile growth. A solid lesion with internal vascular flow is more likely to represent malignancy than a simple cystic anechoic lesion.

Ultrasound scans should be performed every 3-4 months

The optimal interval between surveillance tests depends on the doubling time of the tumour, the duration of detectable pre-clinical disease, acceptability to the family and available resources. Screening intervals of 2, 3, 4, 6 and 12 months are currently occurring in the UK. For surveillance to be effective the screening interval must be such that few cases present clinically between scans (interval tumours). At scanning intervals over 4-6 months several interval tumours have been reported and this is consistent with the estimated WT doubling time (Craft et al. 1999). Therefore we recommend that scans should be undertaken every 3-4 months and no less frequently than 3 times a year. Even at this frequency, occasional tumours may present clinically between scans and families should be made aware of this. However, there is no evidence to suggest that such tumours have worse outcome.

Screening should start at syndrome diagnosis and continue until 5-7 years of age

The duration of screening is dependent on the age range of WT presentation in the predisposition condition. We recommend that surveillance should cover the age range of onset of at least 90-95% of tumours. For all conditions screening should begin at syndrome diagnosis. If a considerable delay is anticipated before molecular confirmation of the diagnosis (for example in Fanconi anaemia-D1) it may be appropriate to undertake a single abdominal ultrasound at presentation and decide whether on-going surveillance is appropriate when the molecular results are available.

For the *WT1* associated syndromes, mosaic variegated aneuploidy syndrome, Fanconi anemia-D1 and Perlman syndrome virtually all tumours occur before 5 years and thus surveillance is not recommended beyond this age. For Beckwith-Wiedemann syndrome screening until 7,8 or 9 years has been advocated (Green et al. 1993; Choyke et al. 1999; McNeil et al. 2002). In the last 30 years in the UK, only one Beckwith-Wiedemann syndrome case registered by the United Kingdom Childhood Cancer Study Group presented with WT after 7 years of age. Therefore, we believe it is reasonable to stop ultrasound surveillance at 7 years for children with 11p15 defects. For Simpson-Golabi-Behmel syndrome there is minimal data available on the age of diagnosis WT, but at least one presented at 7 years, and this condition shows considerable phenotypic overlap with Beckwith-Wiedemann syndrome. Therefore we recommend surveillance should continue until 7 years for children with *GPC3* mutations. Familial WT has the broadest age distribution. Cases linked to *FWT1* have an older age of onset with a median age of presentation of 6 years (Rahman et al. 1998). However, families with very young ages at diagnosis are also known and overall familial WT has a younger mean age at diagnosis than sporadic WT (Breslow et al, 1996). Therefore, we recommend surveillance should continue until 5 years in most families, unless an affected child from the family has presented above this age, in which case it would be reasonable to continue until 7 years. NR would be pleased to discuss any familial WT pedigree.

Management of a screen-detected lesion should take place at a specialist centre

If a suspicious lesion is detected on screening the child should have a repeat ultrasound at a specialist centre. This should be arranged by the referring Geneticist and/or the child's paediatrician. If the repeat ultrasound scan confirms the suspicious lesion specialist radiological and paediatric oncology colleagues should be consulted and further imaging with MRI or CT should be performed. Depending on the size and nature of the lesion it may be decided to repeat imaging at a later date or to proceed to surgery. No treatment should be given until a histologically proven diagnosis of Wilms tumour has been made.

IMPLEMENTATION OF RECOMMENDATIONS

It is likely that many children currently having WT surveillance do not fulfil these recommendations. It would not be appropriate to stop surveillance in such children without discussion with the family. We recommend that children currently in screening should be offered referral to a Geneticist to discuss the recommendations and to decide whether to continue with screening. Some families may wish to continue with screening even if they do not meet the eligibility criteria and may suffer anxiety should surveillance be withdrawn. It may therefore be appropriate to continue screening until 5 years in some children that do not fulfil the eligibility criteria. However, prospectively we recommend that only children with the conditions described should be offered surveillance.

These recommendations are broadly supported by Clinical Geneticists, Paediatric Oncologists and Paediatric Radiologists in the UK. Implementation should result in clarity for patients and clinicians and consistency of practice across the UK. Centralisation of screening through Clinical Genetics services may also allow audit of data on the numbers and outcomes of individuals in screening, which may inform future recommendations. **We request that the attached proforma (Appendix 4) should be completed in all children that are either currently in screening or that are prospectively referred for screening, to facilitate this.**

THE WILMS TUMOUR SURVEILLANCE WORKING GROUP, April 2005

See Appendix 5 for members

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NR would be pleased to be informed of, or to discuss, any Wilms tumour case with any of the cited conditions or other unusual phenotypes.

REFERENCES

- Barbosa AS, Hadjiathanasiou CG, Theodoridis C, Papathanasiou A, Tar A, Merksz M, Gyorvari B, Sultan C, Dumas R, Jaubert F, Niaudet P, Moreira-Filho CA, Cotinot C, Fellous M (1999) The same mutation affecting the splicing of WT1 gene is present or Frasier syndrome patients with or without Wilms' tumor. *Hum Mutat* 13:146-53
- Blik J, Maas SM, Ruijter JM, Hennekam RCM, Alders M, Westerveld A, Mannens M (2001) Increased tumour risk for BWS patients correlates with aberrant H19 and not KCNQ1OT1 methylation: occurrence of KCNQ1OT1 hypomethylation in familial cases of BWS. *Hum Mol Genet* 10:467-76
- Blik J, Gicquel C, Maas S, Gaston V, Le Bouc Y, Mannens M (2004) Epigenotyping as a tool for the prediction of tumor risk and tumor type in patients with Beckwith-Wiedemann syndrome. *J Pediatr* 145:796-9
- Breslow NE, Olson J, Moksness J, Beckwith JB, Grundy P (1996) Familial Wilms tumor: a descriptive study. *Med Ped Oncol* 27:398-403
- Choyke PL, Siegel MJ, Craft A, Green DM, DeBaun MR (1999) Screening for Wilms Tumour in Children with Beckwith-Wiedemann Syndrome or Idiopathic Hemihypertrophy. *Med Pediatr Oncol* 32:196-200
- Coppes M, Campbell CE, Williams BRG (1993) The role of WT1 in Wilms tumorigenesis. *FASEB J* 7:886-95
- Craft AW, Parker L, Stiller C, Cole M (1995) Screening for Wilms tumour in patients with aniridia, Beckwith syndrome or hemihypertrophy. *Med Pediatr Oncol* 24:231-4
- Craft AW (1999) Growth rate of Wilms tumour, *Lancet* 354:1127
- Crolla JA, Cawdery JE, Oley CA, Young ID, Gray J, Fantes J, van Heyningen V (1997) A FISH approach to defining the extent and possible clinical significance of deletions at the WAGR locus. *J Med Genet* 34:207-212
- DeBaun MR, Brown M, Kessler L (1996) Screening for Wilms tumor in children with high-risk congenital syndromes: considerations for an intervention trial. *Med Pediatr Oncol* 27:415-421
- DeBaun MR, Siegel MJ, Choyke PL (1998) Nephromegaly in infancy and early childhood: A risk factor for Wilms tumor in Beckwith-Wiedemann syndrome. *J Pediatr* 132:401-4
- DeBaun MR, Niemitz EL, McNeil DE, Brandenburg SA, Lee MP, Feinberg AP (2002) Epigenetic alterations of H19 and LIT1 distinguish patients with Beckwith-Wiedemann syndrome with cancer and birth defects. *Am J Hum Genet* 70:604-11
- Eccles M, Mason J (2001) How to develop cost-conscious guidelines. *Health Technology Assessment* 5:16

Engel JR, Smallwood A, Harper A, Higgins MJ, Oshimura M, Riek W, Schofield PN, Maher ER (2000) Epigenotype-phenotype correlations in Beckwith-Wiedemann syndrome. *J Med Genet* 37:921-6

Green DM, Breslow NE, Beckwith JB, Norkool P (1993) Screening of children with hemihypertrophy, aniridia and Beckwith-Wiedemann syndrome in patients with Wilms Tumor: A report from the National Wilms Tumor Study. *Med Pediatr Oncol* 12:188-92

Green DM, Grigoriev YA, Nan B, Takashima JR, Norkool PA, D'Angio GJ, Breslow NE (2001) Congestive heart failure after treatment for Wilms tumor. A report from the National Wilms Tumor Study Group. *J Clin Oncol* 19:1926-34

Grundy P, Telzerow P, Paterson MC, Haber D, Berman B, Li F, Garber J (1991) Chromosome 11 uniparental isodisomy predisposing to embryonal neoplasia. *Lancet* 338:1079-80

Hanks S, Coleman K, Reid S, Plaja A, Firth H, FitzPatrick D, Kidd A, Mehes K, Nash R, Robin N, Shannon N, Tolmie J, Swansbury J, Irrthum A, Douglas J, Rahman N (2004) Constitutional aneuploidy and cancer predisposition caused by biallelic mutations in BUB1B. *Nat Genet* 36:1159-61

Hawkins MM, Smith RA (1989) Pregnancy outcomes in childhood cancer survivors: probable effect of abdominal irradiation. *Int J Cancer* 43:399-402

Henneveld HT, van Lingen RA, Hamel BCJ, Stolte-Dijkstra I, van Essen AJ (1999) Perlman syndrome: Four additional cases and review. *Am J Med Genet* 86:439-46

Hoyme HE, Seaver LH, Jones KL, Procopio F, Crooks W, Feingold M. Isolated hemihyperplasia (hemihypertrophy): report of a prospective Multicentre study of incidence of neoplasia and review. *Am J Med Genet* 79:274-8

Jenkinson HC, Hawkins MM, Stiller CA, Winter DL, Marsden HB, Stevens MCG (2004) Long-term population-based risks of second malignant neoplasms. *Br J Cancer* 91:905-10

Kalapurakal JA, Dome JS, Perlman EJ, Malogolowkin M, Haase GM, Grundy P, Coppes MJ (2004) Management of Wilms tumour: current practice and future goals. *Lancet Oncol* 5:37-46

Li M, Shuman C, Ling Fei Y, Cutiongco E, Bender HA, Stevens C, Wilkins-Haug L, Day-Salvatore D, Yong SL, Geraghty MT, Squire J, Weksberg R (2001) GPC3 mutation analysis in a spectrum of patients with overgrowth expands the phenotype of Simpson-Golabi-Behmel syndrome. *Am J Med Genet* 102:161-8

Little M, Wells C (1997) A clinical overview of WT1 gene mutations. *Hum Mutat* 9:209-25

Little S, Hanks S, King-Underwood L, Jones C, Rapley E, Rahman N, Pritchard-Jones on behalf of the UKCCSG (2004) Frequency and heritability of WT1 mutations in 282 non-syndromic Wilms tumour cases. *J Clin Oncol* 22:4140-6

Loirat C, Andre JL, Champigneulle J, Acquaviva C, Chantreau D, Bourguard R, Elion J, Denamur E (2003) WT1 splice site mutation in a 46,XX female with minimal-change nephrotic syndrome and Wilms' tumour. *Nephrol Dial Transplant* 18:823-5

Maher ER and Reik W (2000) Beckwith-Wiedemann syndromes: imprinting in clusters revisited. *J Clin Invest* 105:247-52

Mariani A, Iughetti L, Bertorelli R, Coviello D, Pellegrini M, Forabosco A, Bernasconi S (2003) Genotype/phenotype correlations of males affected by Simpson-Golabi-Behmel syndrome with GPC3 gene mutations: patient report and review of the literature. *J Pediatr Endocrinol Metab* 16:225-32

McDonald JM, Douglass EC, Fisher R, Geiser CF, Krill CE, Strong LC, Virshup D, Huff V (1998). Linkage of familial Wilms tumour predisposition to chromosome 19 and a two-locus model for the etiology of familial tumors. *Cancer Res* 58:1387-90

McNeil D, Brown M, Ching A, DeBaun M (2001) Screening for Wilms tumour and hepatoblastoma in children with Beckwith-Wiedemann syndrome: a cost effective model. *Med Ped Oncol* 37:349-365

Narahara K, Kikkawa K, Kimira S, Kimoto H, Ogata M, Kasai M, Matsuoka K (1984) Regional mapping of catalase and Wilms tumor-aniridia, genitourinary abnormalities, and mental retardation triad loci to the chromosome segment 11p13. *Hum Genet* 66:181-185

Oeffinger KC, Hudson MM (2004) Long-term complications following childhood and adolescent cancer: foundations for providing risk-based health care for survivors. *CA Cancer J Clin* 54:208-236

Pein F, Sakiroglu O, Dahan M, Lebidous J, Merlet P, Shamsaldin A, Villain E, de Vathaire F, Sidi D, Hartmann O (2004) Cardiac abnormalities 15 years and more after adriamycin therapy in 229 childhood survivors of a solid tumour at the Institut Gustave Roussy. *Br J Cancer* 91:37-44

Pritchard-Jones K (2002) Controversies and advances in management of Wilms' Tumour. *Arch Dis Child* 87:241-244

Prorok PC (1992) Epidemiological approach for cancer screening. *Am J Pediatr Hematol/Oncol* 14:117-128.

Rahman N, Arbour L, Tonin P, Renshaw J, Pelletier J, Baruchel S, Pritchard-Jones L, Stratton MR, Narod SA (1996). Evidence for a familial Wilms tumour gene on chromosome 17q12-q21. *Nat Genetics* 13:461-3

Rahman N, Abidi F, Ford D, Arbour L, Rapley E, Tonin P, Barton D, Batcup G, Berry J, Cotter F, Davison V, Gerrard M, Gray E, Grundy R, Hanafy M, King D, Lewis I, Ridolfi Luethy A, Madlensky L, Mann J, O'Meara A, Oakhill T, Skolnick M, Strong L, Variend D, Narod S, Schwartz C, Pritchard-Jones K and Stratton MR (1998) Confirmation of *FWT1* as a Wilms tumour susceptibility gene and phenotypic characteristics of Wilms tumour attributable to *FWT1*. *Hum Genet* 103, 547-56

Rahman N (2005) Mechanisms predisposing to childhood overgrowth and cancer. *Curr Opin Gen Dev* (in press)

Rapley EA, Barfoot R, Bonaiti-Pellie C, Chompret A, Foulkes W, Perusinghe N, Reeve A, Royer-Pokora B, Schumacher V, Shelling A, Skeen J de Turreil A, Weirich A, Pritchard-Jones K, Stratton MR, Rahman N (1998) Evidence for susceptibility genes to familial Wilms tumour in addition to WT1, FWT1 and FWT2. *Br J Cancer*, 83:177-83

Reid S, Renwick A, Seal S, Baskomb L, Barfoot R, Jayatilake H, Familial Wilms Tumour Collaboration, Breast Cancer Susceptibility Collaboration (UK), Pritchard-Jones K, Stratton MR, Ridolfi-Luthy A, Rahman N (2005) Biallelic BRCA2 mutations are associated with multiple malignancies in childhood, including familial Wilms tumour. *J Med Genet* 42:152-8

Royer-Pokora B, Beier M, Henzler M, Alam R, Schumacher V, Weirich A, Huff V (2004) Twenty-four new cases of WT1 germline mutations and review of the literature: genotype/phenotype correlations for Wilms tumor development. *Am J Med Genet* 127A:249-57

Schmidt T, Hohl C, Haage P, Blaum M, Honnef D, Weibeta C, Staatz G, Gunther RW (2003) Diagnostic accuracy of phase-inversion tissue harmonic imaging versus fundamental B-mode sonography in the evaluation of focal lesions of the kidney. *AJR Am J Roentgenol* 180:1639-47.

Schumacher V, Scharer K, Wuhl E, Altrogge H, Bonzel K, Guschmann M, Neuhaus TJ, Pollastro RM, Kuwertz-Broking E, Bulla M, Tondera AM, Mundel P, Helmchen U, Waldherr R, Weirich A, Royer-Pokora B (1998) Spectrum of early onset nephrotic syndrome associated with WT1 missense mutations. *Kid Int* 53:1594-1600

Stiller CA (2004) Epidemiology and genetics of childhood cancer. *Oncogene* 23:6429-44

Tischkowitz MD and Hodgson SV (2003) Fanconi Anemia. *J Med Genet* 40:1-10

Weksberg R, Smith AC, Squire J, Sadowski P (2003) Beckwith-Wiedemann syndrome demonstrates a role for epigenetic control of normal development. *Hum Mol Genet* 12:R61-8

West PM, Love DR, Stapleton PM, Winship IM (2003) Paternal uniparental disomy in monozygotic twins discordant for hemihypertrophy. *J Med Genet* 40:223-6

Wiedemann HR (1983). Tumors and hemihypertrophy associated with Wiedemann-Beckwith syndrome. *European Journal of Pediatrics*:141:129

APPENDIX 1: GRADING SCHEME

The grading scheme and hierarchy of evidence used was adapted from Eccles and Mason (2001)

Recommendation Grade	Evidence
A	Directly based on category I evidence
B	Directly based on: <ul style="list-style-type: none"> • Category II evidence, or • Extrapolated recommendation from category I evidence
C	Directly based on: <ul style="list-style-type: none"> • Category III evidence, or • Extrapolated recommendation from category I or II evidence
D	Directly based on: <ul style="list-style-type: none"> • Category IV evidence, or • Extrapolated recommendation from category I, II or III evidence
Evidence category	Source
I	Evidence from: <ul style="list-style-type: none"> • meta-analysis of randomised controlled trials, or • at least one randomised controlled trial
II	Evidence from: <ul style="list-style-type: none"> • at least one controlled study without randomisation, or • at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

APPENDIX 2: STAGE AND RISK CLASSIFICATION FOR WILMS TUMOUR

Stage	Proportion of cases	Tumour
I	45-50%	Tumour limited to one kidney and totally excised, renal capsule intact, no residual tumour apparent.
II	20%	Regional tumour extension beyond the kidney but totally excised. No residual tumour apparent.
III	10-15%	Residual non-haematogenous tumour confined to the abdomen.
IV	15%	Blood-borne metastases (eg lung, liver, bone, brain).
V	5%	Bilateral tumours at diagnosis.
Risk Classification	Proportion of cases	Histology
Low-risk	~5-10%	Cystic partially differentiated nephroblastoma Completely necrotic nephroblastoma
Intermediate risk	~70-80%	Nephroblastoma – epithelial type Nephroblastoma – stromal type Nephroblastoma – mixed type Nephroblastoma – regressive type Nephroblastoma – focal anaplasia
High risk	~15-20%	Nephroblastoma – blastemal type Nephroblastoma – diffuse anaplasia

APPENDIX 3: LABORATORIES IN UK OFFERING MOLECULAR TESTING FOR WT-ASSOCIATED CONDITIONS

NHS Diagnostic Testing (please contact relevant centre for the cost of tests)

- WT1 deletions (FISH)
Wessex Regional Genetics Laboratory, Salisbury District Hospital, Salisbury Health Care NHS Trust, Wiltshire, SP2 8BJ. Tel: 01722 429080
- WT1 mutations
North Trent Molecular Genetics Service, Western Bank, Sheffield, S10 2TH. Tel: 0114 2717003
- BRCA2 mutations
Several laboratories across the country (screening of the full gene should be performed)
- 11p15 uniparental disomy and/or loss of methylation at KvDMR1
West Midlands Regional Genetics Service, Birmingham Women's Hospital, Edgbaston, Birmingham, B15 2TG. Tel: 0121 6272710
Wessex Regional Genetics Laboratory, Salisbury District Hospital, Salisbury Health Care NHS Trust, Wiltshire, SP2 8BJ. Tel: 01722 429080
- GPC3 mutations and deletions
Northern Genetics Service, Institute of Human Genetics, International Centre for Life, Central Parkway, Newcastle upon Tyne, NE1 3BZ. Tel: 0191 2418754

Research Testing (no charge)

- BUB1B mutations
- BRCA2 mutations
- Familial Wilms tumour investigations
- Hemihypertrophy / asymmetric growth cases (we will perform 11p15 analyses)
- Investigation of unusual Wilms tumour phenotypes

All performed at Section of Cancer Genetics, Institute of Cancer Research, Sutton, Surrey, SM2 5NG (contact Nazneen Rahman Tel: 0208 7224026 email: nazneen.rahman@icr.ac.uk)

APPENDIX 4: PROFORMA FOR AUDIT OF WILMS TUMOUR SURVEILLANCE

Centre/Hospital:

Reference/Hospital Number:

Dob of proband:

Diagnosis:

Relevant Clinical History:

Relevant Family History:

Age referred for US screening:

Age (or projected age) that US screening stopped (will stop):

How often was/will screening be undertaken:

Has the child developed a tumour, if so what tumour:

Age developed tumour:

Was tumour screen-detected:

If no, was the child in screening:

If yes, how long before tumour diagnosis was the last screen:

Contact details of person completing form:

Please add any additional information overleaf

Please return to :

Nazneen Rahman

Section of Cancer Genetics

Institute of Cancer Research

15 Cotswold Road

Sutton, Surrey, SM2 5NG

Tel 0208 722 4026, Fax 0208 722 4359

Email nazneen.rahman@icr.ac.uk

Thank you for completing this form

APPENDIX 5: THE WILMS TUMOUR SURVEILLANCE WORKING GROUP

Professor Nazneen Rahman (Chair)

Professor of Childhood Cancer Genetics and Honorary Consultant in Medical Genetics, Institute of Cancer Research, Sutton.

Professor Alan Craft

Consultant Paediatrician, Royal Victoria Infirmary, Newcastle-Upon-Tyne

Dr Ian Kenney

Consultant Radiologist, Royal Alexandra Hospital for Sick Children, Brighton

Dr Gill Levitt

Consultant in oncology and late effects, Great Ormond Street Hospital for Children NHS Trust, London

Professor Eamonn Maher

Professor and Honorary Consultant in Medical Genetics, Birmingham Women's Hospital, Birmingham

Dr Øystein E. Olsen

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We are grateful to the many other people that made very valuable contributions to the discussions leading to this document.