Towards evidence based medicine for paediatricians

Edited by Bob Phillips

In order to give the best care to patients and families, paediatricians need to integrate the highest quality scientific evidence with clinical expertise and the opinions of the family. Archimedes seeks to assist practising clinicians by providing “evidence based” answers to common questions which are not at the forefront of research but are at the core of practice. In doing this, we are adapting a format which has been successfully developed by Kevin Macaway-Jones and the group at the Emergency Medicine Journal—“BestBets”.

A word of warning. The topic summaries are not systematic reviews, through they are as exhaustive as a practising clinician can produce. They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature. What Archimedes offers are practical, best evidence based answers to practical, clinical questions.

The format of Archimedes may be familiar. A description of the clinical setting is followed by a structured clinical question. (These aid in focusing the mind, assisting searching, and gaining answers.) A brief report of the search used follows—this has been performed in a hierarchical way, to search for the best quality evidence to answer the question. A table provides a summary of the evidence and key points of the critical appraisal. For further information on critical appraisal, and the measures of effect (such as number needed to treat, NNT) books by Sackett and Moyer may help. To pull the information together, a commentary is provided. But to make it all much more accessible, a box provides the clinical bottom lines.

Electronic-only topics that have been published on the BestBets site (www.bestbets.org) and may be of interest to paediatricians include:

- What is the use of smectite in acute diarrhoeal illnesses?
- Are the Ottawa ankle rules helpful in ruling out the need for x-ray examination in children?
- Can transcutaneous bilirubinometry reduce the need for serum bilirubin estimations in term and near term infants?
- What is the risk of cancer in a child with hemihypertrophy?

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REFERENCES


Test/don’t test?

It’s been the misfortune of every living doctor, and those no longer with us, to pick up the result of a test they’ve ordered and wish they’d never signed the request in the first place. The test result is there, you understand what it means (technically), but also struggle with what it means (practically) to the patient before you. There are psychic echoes of radiology consultations, “and how with this x-ray result change your management?”, and you wish you’d internally digested what was being said.

In diagnostic testing, we hope to reach a state where we are adequately convinced of the presence or absence of a condition, so that we may either treat it, test for it, or no longer worry about it. This instinctive process can be thought of as creating two lines in the shifting sands of diagnosis and working out where we now stand. Above one line, you’re certain enough of the diagnosis to treat. Below the other line, you’re convinced of the condition’s absence, and so need not consider it any further. Between the two there is an uncertainty that requires some form of “test”.

The upper threshold is created based on the risk versus benefits of a treatment, and so how certain you need to be about a diagnosis before you begin therapy. To take two extreme examples: one needs to be absolutely certain before embarking on a course of chemotherapy and/or radiotherapy that the lump you’re dealing with is a sarcoma. On the other hand, you don’t have to be that convinced that a child is suffering from a viral coryzal illness before you prescribe paracetamol.

The lower threshold is drawn when you are convinced that the chance of disease, and consequence of not investigating further at this point, are so low as to require no more action. The child with acute shotty cervical nodes and tonsillitis is extremely unlikely to have lymphoma, and wouldn’t require biopsy. (It’s not that the diagnosis is impossible—just that the balance of risk:harm weighs against excision biopsy for every child with tonsillitis and cervical lymphadenopathy.)

In between these thresholds is where you would test. But your test (or series of tests) needs to be good enough to either push you into a convincing denial of the disease, or enough evidence to commence therapy. (It shouldn’t be forgotten that in many instances we use “waiting” as our chosen test.)

Where the evidence comes into this mix is in refining the balance of benefits versus harms (for more on this, see Phillips) and demonstrating how good a test is in its ability to move you up towards treatment, or down towards exclusion (for more on likelihood ratios, see Phillips). What it can’t do is rescue you from the test whose accuracy you don’t know about in a patient whose chance of disease you hadn’t thought about.

This month’s Archimedes helps us along the path of diagnosis by exploring the clinical examination (for ankle fractures), technical aids to examination (for jaundice), and the risk:benefit of testing (in isolated hemi-hypertrophy). Where we draw our lines is based on clinical expertise, experience, and the attitude of the family we’re dealing with.

References

Are the Ottawa ankle rules helpful in ruling out the need for x-ray examination in children?

Report by
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doi: 10.1136/adc.2004.066647

The Ottawa ankle rules (OAR) are a set of guidelines to help the physician as to decision making regarding need for x-ray examination after ankle and mid-foot injury. A previous best evidence topic report examined whether these rules could be applied to children. At that time there was insufficient evidence to make a determination. This appraisal updates that topic.

Structured clinical question
In a child with history of ankle injury [patient] are the Ottawa ankle rules [test] reliable in eliminating the need for x-ray examination in some patients without the risk of missing fractures [outcome]?

Search strategy and outcome
Secondary sources
Cochrane—two trials that involved children were found in Central.

Primary sources
PubMed—(Clinical Queries) Ottawa ankle rules AND child.

One systematic review was found that included 27 studies, six of which were pertaining to children, two of which were the trials found in Central. Eight total prospective studies were found; six were those included in the systematic review plus two subsequent publications.

Search outcome
Eight relevant papers found. See table 1.

Commentary
The physical examination findings for the Ottawa ankle rules are as follows: tenderness over the lateral malleoli, inability to bear weight, and tenderness over the posterior distal tibia and fibula. A patient that exhibits one of these characteristics is deemed in need of x-ray examination. The OAR have been validated for use as a screening tool in adults who have sustained ankle or mid-foot injuries. Three considerations render the applicability of OAR to children less certain. Children may not be as reliable with regard to verbal history. Because Salter-Harris type I fractures, defined as a separation of bone >3 mm through the physes, more commonly accompany trauma in infants and children, point tenderness will generally be present. Further, a child must be able to walk freely prior to injury, in order for the OAR to be applied. Thus the OAR criteria will be positive and unnecessary radiographs may be obtained for an injury that will ultimately be treated the same as a sprain.

Data analysis
We computed a random effects meta-analysis model directly on the proportions with weights based on the variance of a binomial distribution. We used a pooled estimate of sensitivity/specificity, instead of individual sensitivities/specificities for each study. Statistical calculations were made using the meta library, version 0.5, with the R software package, version 2.01 (R Foundation for Statistical Computing, Vienna, Austria).

Formulas from Evidence-Based Medicine text by Sackett were used to calculate prevalence, likelihood ratios, post-test odds, PPV, and NPV.

Main results
The overall sensitivity was calculated to be 97% with confidence limits of 93%–100%. The overall specificity was calculated to be 29% with confidence limits of 18%–40%.

An estimated prevalence of 12% was calculated based on the number of fractures in the studies divided by the total number of patients. The prevalence and likelihood ratio were then used to derive the PPV and NPV.

There was one article4 that showed five patients with negative results when applying the rules who ultimately had a fracture. All other articles had zero or 1 in this category. Using the Ottawa ankle rules has relevance in the clinical setting; as it is a tool that can be used to aid the clinician in decreasing unnecessary x-ray examinations. This may very well decrease patient care costs, as well as patient time spent in the acute care setting.

A small percentage of patients that are excluded from receiving x-ray evaluation based on the Ottawa ankle rules, will actually have a fracture. It is a low percentage of patients at 1.4%. These missed fractures will often be of little clinical significance, as many of them will represent the Salter-Harris I classification. While there may be no long term consequences to these missed fractures, each clinician must decide their comfort level in applying the rules to individual patients.

CLINICAL BOTTOM LINE

- These rules are meant to be applied to those patients who have the ability to walk prior to their injury, and can localise pain with verbal communication. (grade A)
- Negative results when applying the rules should help the physician to decrease x-ray usage without an increase in missed fractures. (grade A)
- For every 1000 patients that exhibit negative Ottawa ankle rules, 14 will actually have fractures. (grade A)

REFERENCES
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<th>Methods</th>
<th>Key results</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Important notes</th>
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<tr>
<td>Boutis et al (2001)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>607 patients evaluated ages 3–16 years old</td>
<td>Blinded prospective study in 2 similar urban emergency departments with fellows and attending staff as participants. Instruction on the use of OAR was given by orthopaedic surgeons prior to start of study</td>
<td>Sensitivity 100% (95% CI = 0.96–1.0) Specificity 13% (95% CI = 0.11–0.16)</td>
<td>Isolated ankle trauma within 72 hours of injury</td>
<td>Age &lt;3 years and &gt;16 years, preexisting musculoskeletal disease, coagulopathy, developmental delay, previous history of surgery or recent &lt;3 months injury of affected ankle or multi-system trauma</td>
<td>Patients were divided into low risk and high risk groups. Low risk consisted of isolated pain, tenderness, or both with or without oedema or ecchymosis of the distal fibula below the level of the joint line of the ankle. All other findings were classified as high risk. They also assessed the potential for reduction in radiographs when comparing the low risk clinical findings with those obtained by combining the Ottawa ankle rules.</td>
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<td>Chande (1995)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>68 patients evaluated ages 2–18 years old</td>
<td>Prospective survey with 24 variables obtained by physicians; x-rays were taken of all study participants with blinding of investigator to results of x-rays when applying OAR to evaluate for qualification of a x-ray</td>
<td>Sensitivity 100% (95% CI = 0.77–1.0) Specificity 32% (95% CI = 0.21–0.43)</td>
<td>All types of fractures</td>
<td>Open fractures, patients without follow up</td>
<td>Small sample size</td>
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<td>Clarke and Toner (2003)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>160 patients evaluated ages 0–18 years old</td>
<td>Prospective survey with 22 variables; x-rays were obtained on all patients with radiologists being blinded to survey results</td>
<td>Sensitivity 83% (95% CI = 0.65–0.94) Specificity 50% (95% CI = 0.41–0.58)</td>
<td>All types of fractures</td>
<td>Age &gt;18, intoxication, previous films, pregnancy, suspected physical abuse, open fractures, OI, metabolic disease, patient’s without phone contact, neurologic impairment</td>
<td>There was only case in a child &lt;5 years that was a true negative for rules and fracture, and no true positives</td>
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<td>Cuello-Garcia et al (2004)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>111 patients evaluated ages 3–18 years</td>
<td>Prospective evaluation by paediatric nurses, third year residents, and attendings in the ER. OAR was applied, and x-rays obtained at physician discretion. Radiology was blinded to OAR results</td>
<td>Sensitivity 100% (95% CI = 0.95–1.0) Specificity 6% (95% CI = 0.01–0.11)</td>
<td>Salter-Harris II–V</td>
<td>Multiple trauma, &gt;7 days from event, changes in consciousness, bony disease, patients who came for reevaluation, Salter-Harris I fractures</td>
<td>Salter-Harris I fractures were not included; there were 18 of these total. Patients were followed up at one month with telephone calls, and none of the patients showed later complications or changes in the diagnosis</td>
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<td>Karpas et al (2002)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>190 patients evaluated ages 5–19 years</td>
<td>Blinded cross-sectional study that implemented OAR after two nurse training sessions</td>
<td>Sensitivity 96% (95% CI = 0.82–0.99) Specificity 27% (95% CI = 0.18–0.32)</td>
<td>Patients who presented within 48 hours of injury and all fractures</td>
<td>Open fracture, multiple traumas, developmental delay, referral with x-ray, recurrent visits for the same injury in the last 2 weeks</td>
<td>Study included one patient with Salter-Harris I and negative rules</td>
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<td>Libetta et al (1999)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>761 patients evaluated ages 1–15 years</td>
<td>A historical control group was included prior to the implementation of OAR in this prospective evaluation as a comparison to predict need for x-ray</td>
<td>Sensitivity 98% (95% CI = 0.95–1.0) Specificity 46% (95% CI = 0.43–0.51)</td>
<td>Patients that had ability to walk prior to injury</td>
<td>Patients were excluded in August in order to give the staff one month to learn and implement the Ottawa ankle rules</td>
<td>Small number of children &lt;5 years old. Total of 57 children out of 761 patients. Mid-foot injuries were included in this study</td>
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<td>McBride (1997)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>37 patients evaluated ages 9–15 years</td>
<td>Prospective survey looking at the ability of OAR to decrease need for x-ray after instructing family practitioners in the ER setting on the use of these rules</td>
<td>Sensitivity 100% (95% CI = 0.87–1.0) Specificity 28% (95% CI = 0.14–0.39)</td>
<td>Fracture &gt;3 mm</td>
<td>Pregnancy, open injury, presentation &gt;1 week after injury, enrolment one time per patient</td>
<td>Small study, no children &lt;9 years old and only five were younger than 12 years old. This limited the issue of growth plate fractures</td>
</tr>
<tr>
<td>Plint et al (1999)&lt;sup&gt;9&lt;/sup&gt;</td>
<td>670 patients evaluated ages 2–16 years</td>
<td>Patients were evaluated by staff and fellows trained in OAR at two hospital EDs; x-rays were obtained based on each hospital’s practices. Data forms with physical exam findings were filled out prior to viewing the x-ray. The principal investigator reviewed the data forms and made a decision regarding positive or negative OAR</td>
<td>Sensitivity 100% (95% CI = 0.58–1.0) Specificity 27% (95% CI = 0.11–0.42)</td>
<td>Present with injury within 48 hours, fractures &gt;3 mm</td>
<td>Salter-Harris I, nonsignificant fractures defined as &lt;3 mm, &lt;2 years old, multiple injuries, obvious open fractures, neurovascular compromise, diseases predisposing to fractures (OIL, underlying disease with sensory/neural abnormalities (spina bifida), isolated injuries of the skin, patients returning for reassessment of the same injury, patients referred to the ED with x-rays, intoxication</td>
<td>119 Salter-Harris I fractures, 32 nonsignificant fractures [*when calculating the 2 × 2 table, 96 patients were counted twice (once for ankle fractures and a second time for foot fracture) therefore the N in this study was 766]. Mid-foot injuries were included in this study</td>
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*Note: OAR = Ottawa Ankle Rules, ED = Emergency Departments, CI = Confidence Interval.*
Can transcutaneous bilirubinometry reduce the need for serum bilirubin estimations in term and near term infants?

Report by
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While doing a discharge check on a 3 day old baby, a paediatric SHO notices mild jaundice and prepares to perform a serum bilirubin estimation (SBR). She explains this to the mother, who breaks into tears and asks the SHO if there was any way she could check the level of jaundice without doing a blood test. The SHO discusses this with the neonatal consultant who mentions “We used to have a transcutaneous bilirubinometer when I was an SHO, but we stopped using it because it was inaccurate”.

A more sympathetic registrar gives you a recent review article1 on jaundice which indicates that the older generation bilirubinometers were shown to be inaccurate for clinical use; however, a newer version, the “SpectRx Bilicheck” may be more reliable. Bilicheck (BC) uses multiple wavelengths of light, and the manufacturer claims that the monitor is unaffected by skin pigmentation and other interfering factors.

You wonder if the Bilicheck could be safely used as a screening test for jaundice on the postnatal wards.

Structured clinical question
In term or near term healthy newborn babies [population] can transcutaneous bilirubinometry [test] when compared with serum bilirubin estimation [gold standard] accurately identify all cases of significant jaundice (i.e. >250 µmol/l)?

Search strategy and outcome
We searched PubMed under clinical queries and diagnosis using keyword “Bilicheck”, which identified three studies, all of which were of good quality. See table 2.

Commentary
We intended to use transcutaneous assessment on the postnatal ward as a screening test. It was important that the Bilicheck would not miss any significant jaundice. We arbitrarily chose 250 µmol/l (a level below which an intervention would be unlikely to be term in near term babies after 24 hours). We wanted to determine if Bilicheck had a high sensitivity at this SBR level, so that babies would not need a blood test if Bilicheck value was less than 250 µmol/l.

Bilirubin values were converted to SI units (µmol/l) (1 mg = 17.1 µmol/l) for easiness of comparison.

The review is confined to three good quality studies identified following a basic PubMed search. The first two studies compared Bilicheck with the internationally accepted gold standard for bilirubin estimation2–4 (that is, high performance liquid chromatography) and found that it was at least as good as laboratory method.

Even though all studies showed good correlation between the Bilicheck readings and laboratory values, it was more important to establish that no cases of significant jaundice would be missed when it is used as a screening test.

Considering bilirubin levels of >250 µmol/l as significant jaundice, it appears that Bilicheck can be used to exclude

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<tr>
<td>Bhutani et al (2000)2</td>
<td>490 term and near term (&gt;35 weeks, &gt;2 kg) up to 4 days. Gold standard = high performance liquid chromatography (HPLC)</td>
<td>Prospective cohort</td>
<td>Sensitivity and specificity on comparison with gold standard specific centile chart used</td>
<td>For picking up SBR &gt;256 µmol/l (95th centile) Sensitivity 100%, Specificity 88%. All babies with SBR &lt;40th centile had BC &lt;40th centile</td>
<td>Only 3.1% had SBR &gt;256 µmol/l Bilicheck was as accurate as standard laboratory measurement No babies with significant jaundice would be missed All newborns at discharge had SBR check irrespective of clinical jaundice</td>
</tr>
<tr>
<td>Rubatelli et al (2001)3</td>
<td>Newborns &gt;30 weeks and &lt;28 days, 210 infants in 6 European hospitals recruited. HPLC as gold standard</td>
<td>Prospective cohort</td>
<td>Sensitivity and specificity on comparison with gold standard</td>
<td>At HPLC cut off 222 µmol/l, BC had a sensitivity and specificity of 93% and 73%. and while standard lab method had sensitivity and specificity of 95% and 76% At HPLC of 290 µmol/l BC and standard lab method had sensitivity and specificity of 90%/87% and 87%/83%</td>
<td>BC more accurate than standard lab SBR especially at higher values Independent of race, gestation, and weight</td>
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<tr>
<td>Samanta et al (2004)4</td>
<td>300 term and near term newborn babies Standard laboratory method</td>
<td>Prospective cohort</td>
<td>Sensitivity and specificity on comparison with gold standard</td>
<td>91% sensitivity and 66% specificity in diagnosing significant jaundice (i.e. &gt;250 µmol/l)</td>
<td>55% reduction in blood sampling would have occurred if Bilicheck was used as a screening tool 5 babies with significant jaundice (&gt;250 µmol/l) were missed. But all the 5 had SBR &lt;300 µmol/l</td>
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What is the risk of cancer in a child with hemihypertrophy?

Report by
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doi: 10.1136/adc.2005.082792

You have a 4 year old girl with hemihypertrophy limited to the left leg in your clinic come for review. This child was originally referred to your clinic a few weeks back after her mother noticed length discrepancy when she bought a new pair of trousers. You notice asymmetry between the two legs, with the left leg larger and longer than the right. An orthopaedic surgeon was consulted, who ruled out a hip problem and suggested the possibility of hemihyperplasia of the left leg. There is an increased risk of cancer, especially of Wilms’ tumour in these children, and hence a paediatric surgeon was consulted. Ultrasound scan of abdomen ruled out Wilm’s tumour in these children, and hence a paediatric orthopaedic surgeon was consulted, who ruled out a hip problem and suggested the possibility of hemihypertrophy.

Structured clinical question
In a child with hemihyperplasia limited to the left leg [subject] what is the risk of cancer [outcome] and what is the best follow up plan [intervention] for early detection of these cancers?

Search strategy and outcome
Cochrane database
No relevant articles found.

Medline database (1996 to date and 1951 to date)
Hemihypertrophy or hemi hyperplasia, tumours or neoplasm, follow up ultrasound scans; 11 related articles, one was relevant which was a case series analysis of screening for Wilm’s tumour in children with Beckwith-Wiedemann syndrome (BWS)/idiopathic hemihypertrophy (HH)5 (table 3).

PubMed
Four searches: hemi hypertrophy, hemi hyperplasia, tumours in hemihyperplasia, hemihypertrophy and review or follow up. Limits: birth to 18 years, human. Two relevant studies identified. One was excluded as there were only 12 patients in the series. The other one was a prospective multicentre study of incidence of neoplasia and review in isolated hemihyperplasia6 (table 3).

Commentary
Hemihypertrophy is also known as hemihyperplasia. The terminology hemihyperplasia seems more accurate as the pathological process involves an abnormal proliferation rather than an increase in the size of these cells.1 Asymmetric overgrowth of unknown aetiology may involve the whole of one side of the body or it may be limited in extent to one limb or a side of the face. There may be associated asymmetric hypertrophy of internal organs. The reported incidence of hemihyperplasia is 1 in 86 000 live births.2 Hemihyperplasia may be an isolated finding or it may be associated with other syndromes such as Beckwith-Wiedmann, Klippel-Trenaunay-Weber, or McCune-Albright syndromes.

Predisposition to neoplasia (cancer) in isolated hemihyperplasia is well known, but the exact risk is not well documented. Green and colleagues2 in 1993 reported that only in one third of cases of children with Wilms’ tumour and hemihyperplasia, was the hyperplasia diagnosed more than a month prior to the discovery of the tumour.

The case series by Choyke and colleagues3 concluded that children with BWS/HH may benefit from screening abdominal ultrasound scans at intervals of four months or less, but false positive screening results may lead on to unnecessary surgery and suggested a larger prospective study to determine if the benefits of screening outweigh the risk. It was difficult to draw a conclusion from this case series with regard to isolated HH alone as this case series involved a mixture of BWS and HH cases. Also the sample size, especially of the screened group, was too small.

The only multicentre prospective study looking at the risk of tumour development and follow up of children with hemihyperplasia was the one carried out by Hoyne and colleagues.4 In this study, of the total 168 children with isolated hemihyperplasia, 10 tumours developed in nine children (one child developed two tumours). Of these, six were Wilms’ tumour, two were adrenal cell carcinoma, and there was one each of hepatoblastoma and leiomysarcoma of the small bowel. Follow up protocols varied in different centres. Two children, an infant and a 5 year old, developed Wilms’ tumours at nine month and five months respectively after their previous abdominal ultrasound scan. This led the investigators to conclude that six months may be too long a screening interval, especially in early childhood.
Hence from the available evidence, the risk of tumour development in isolated hemihyperplasia is about 1 in 20 or approximately 5%. The best follow up plan on the basis of available evidence is that till the age of 6 years these children should have abdominal ultrasound scans at three monthly intervals. There is currently insufficient evidence to screen children above 6 years of age.

**REFERENCES**


**Table 3 Follow up and outcome of children with hemihyperplasia**

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<th>Citation</th>
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<th>Study type</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
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<tr>
<td>Hoyme et al (1998)</td>
<td>168 children</td>
<td>Prospective multicentre study</td>
<td>Tumour development on</td>
<td>Tumour incidence 5.9% (95% CI 2.3%–8.2%) compared to 0.17% in general</td>
<td>Prospective multicentre study, over 10 year period. Relatively large</td>
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<td></td>
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<td>of incidence of neoplasia and</td>
<td>follow up abdominal</td>
<td>population; follow up protocol varied among respondents; mostly</td>
<td>number of patients (with a rare condition). No control group</td>
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<td>follow up over 10 year period</td>
<td>ultrasound</td>
<td>abdominal palpation 6–12 monthly and USS abdomen 6 monthly</td>
<td>Varied follow up protocols, varied duration of follow ups; tumour</td>
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<td>surveillance protocol suggested; abdominal USS 3 monthly till</td>
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<td>6 years of age and 6 monthly afterwards until puberty</td>
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<td>Choyke et al (1999)</td>
<td>74 children</td>
<td>Case series comparing late stage</td>
<td>Follow up sonograms;</td>
<td>None of the screened (n = 14) had late stage (stage III or IV) Wilm’s</td>
<td>Case series</td>
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<td>Wilm’s tumour in patients with</td>
<td>tumour development</td>
<td>tumour whereas 25 out of the 59 unscreened had late stage disease;</td>
<td>Both BWS and HH included in the study and hence difficult to</td>
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<td>BWS/HH who are screened with</td>
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<td>benefit from sonograms at intervals of 4 months or less</td>
<td>correlate risk of tumour development and screening to isolated HH alone</td>
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<td>ultrasound scans (4 monthly)</td>
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<td>Small sample size, especially the screened group</td>
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<td>against those who are not</td>
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**CLINICAL BOTTOM LINE**

- Risk of tumour development in children with isolated hemihyperplasia is 5.9%. (95% CI 2.3%–8.2%); approximately 5% or 1 in 20. (grade A)
- The best follow up plan for these children is to do abdominal ultrasound scans at three monthly intervals until the age of 6 years. (grade C)
- Further clinical trials are needed to find the benefit of screening children older than 6 years of age as there is currently insufficient evidence to justify screening these children.