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## Clinical and molecular diagnosis, screening and management of Beckwith–Wiedemann syndrome: an international consensus statement

Frédéric Brioude<sup>1</sup>, Jennifer M. Kalish<sup>2</sup>, Alessandro Mussa<sup>3,4</sup>, Alison C. Foster<sup>5,6</sup>, Jet Blik<sup>7</sup>, Giovanni Battista Ferrero<sup>3</sup>, Susanne E. Boonen<sup>8</sup>, Trevor Cole<sup>5</sup>, Robert Baker<sup>9</sup>, Monica Bertoletti<sup>10</sup>, Guido Cocchi<sup>11</sup>, Carole Coze<sup>12</sup>, Maurizio De Pellegrin<sup>13</sup>, Khalid Hussain<sup>14</sup>, Abdulla Ibrahim<sup>15</sup>, Mark D. Kilby<sup>16</sup>, Malgorzata Krajewska-Walasek<sup>17</sup>, Christian P. Kratz<sup>18</sup>, Edmund J. Ladusans<sup>19</sup>, Pablo Lapunzina<sup>20</sup>, Yves Le Bouc<sup>1</sup>, Saskia M. Maas<sup>7</sup>, Fiona Macdonald<sup>21</sup>, Katrin Öunap<sup>22</sup>, Licia Peruzzi<sup>23</sup>, Sylvie Rossignol<sup>24</sup>, Silvia Russo<sup>25</sup>, Caroleen Shipster<sup>26</sup>, Agata Skórka<sup>17,27</sup>, Katrina Tatton-Brown<sup>28</sup>, Jair Tenorio<sup>20</sup>, Chiara Tortora<sup>29</sup>, Karen Grønskov<sup>30</sup>, Irène Netchine<sup>1</sup>, Raoul C. Hennekam<sup>31</sup>, Dirk Prawitt<sup>32</sup>, Zeynep Tümer<sup>30</sup>, Thomas Eggermann<sup>33</sup>, Deborah J. G. Mackay<sup>34</sup>, Andrea Riccio<sup>35</sup>, and Eamonn R Maher<sup>36</sup>

<sup>1</sup>Sorbonne Universités, UPMC Univ Paris 06, INSERM UMR\_S938 Centre de Recherche Saint-Antoine (CRSA), APHP hôpital Trousseau, Explorations Fonctionnelles Endocriniennes, 26 avenue du Docteur Arnold Netter, F-75012 Paris, France <sup>2</sup>Division of Human Genetics, Children's Hospital of Philadelphia and the Department of Pediatrics at the Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA <sup>3</sup>Department of Public Health and Pediatric Sciences, University of Torino, Torino, Via Verdi, 8 - 10124 Torino Italy <sup>4</sup>Neonatal Intensive Care Unit, Department of Gynaecology and Obstetrics, S. Anna Hospital, Città della Salute e della Scienza di Torino, Via Ventimiglia, 3, 10126, Italy <sup>5</sup>Birmingham Health Partners, West Midlands Regional Genetics Service, Birmingham Women's and Children's NHS Foundation Trust, B15 2TG, UK <sup>6</sup>Institute of Cancer and Genomic Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT UK <sup>7</sup>Department of Clinical Genetics, Academic Medical Center, University of Amsterdam, PO Box 7057 1007 MB

Correspondence to E.R.M. erm1000@medschl.cam.ac.uk.

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### Further information

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Amsterdam, Netherlands <sup>8</sup>Clinical Genetic Unit, Department of Pediatrics, Zealand University Hospital, Sygehusvej 10 4000 Roskilde, Denmark <sup>9</sup>Beckwith-Wiedemann Support Group UK, The Drum & Monkey, Wonston, Hazelbury Bryan, Sturminster Newton, Dorset, DT10 2EE <sup>10</sup>Italian Association of Beckwith-Wiedemann syndrome (AIBWS) Piazza Turati, 3, 21029, Vergiate (VA) <sup>11</sup>Ima Mater Studiorum, Bologna University, Via Zamboni, 33- 40126 Bologna BO, Italy <sup>12</sup>Aix-Marseille Univ et APHM, Hôpital d'Enfants de La Timone, Service d'Hématologie-Oncologie Pédiatrique, 264 Rue Saint Pierre, 13385 Marseille, France <sup>13</sup>Pediatric Orthopaedic Unit IRCCS Ospedale San Raffaele, Milan, Via Olgettina Milano, 60, 20132 Milano MI, Italy <sup>14</sup>Department of Paediatric Medicine, Division of Endocrinology, Sidra Medical & Research Center, Al Gharrafa St, Ar-Rayyan, Qatar, Doha <sup>15</sup>Department of Plastic and Reconstructive Surgery, North Bristol NHS Trust, Southmead Hospital, Bristol BS10 5NB, UK <sup>16</sup>Centre for Women's and Children's Health, University of Birmingham and Birmingham Women's and Children's NHS Foundation Trust, Birmingham, B4 6NH, UK <sup>17</sup>Department of Medical Genetics, The Children's Memorial Health Institute, 20, 04-730, Warsaw, Poland <sup>18</sup>Pediatric Hematology and Oncology, Hannover Medical School, Carl-Neuberg- Straße 1 30625, Hannover, Germany <sup>19</sup>Department of Paediatric Cardiology, Royal Manchester Children's Hospital, Manchester, M13 8WL UK <sup>20</sup>Instituto de Genética Médica y Molecular (INGEMM)-IdiPAZ, Hospital Universitario La Paz-UAM Paseo de la Castellana, 261, 28046 and CIBERER, Centro de Investigación Biomédica en Red de Enfermedades Raras, ISCIII, Calle de Melchor Fernández Almagro, 3, 28029, Madrid, Spain <sup>21</sup>West Midlands Regional Genetics Laboratory, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, B15 2TG UK <sup>22</sup>Department of Clinical Genetics, United Laboratories, Tartu University Hospital and Department of Clinical Genetics, Institute of Clinical Medicine, University of Tartu, L. Puusepa 2, 51014, Tartu, Estonia <sup>23</sup>AOU Città della Salute e della Scienza di Torino, Via S. Francesco da Paola, 31, 10123 Torino TO, Italy; Regina Margherita Children's Hospital, Piazza Polonia, 94, 10126 Torino TO Italy <sup>24</sup>Service de Pédiatrie, Hôpitaux Universitaires de Strasbourg, Laboratoire de Génétique Médicale, INSERM U1112 Avenue Molière 67098 STRASBOURG Cedex, Fédération de Médecine Translationnelle de Strasbourg (FMTS), Université de Strasbourg, 4 Rue Kirschleger, 67000 Strasbourg, France <sup>25</sup>Medical Cytogenetics and Molecular Genetics Laboratory, Centro di Ricerche e Tecnologia Biomediche IRCCS, Istituto Auxologico Italiano, Via Zucchi 18, 20095 Cusano, Milan, Italy <sup>26</sup>Great Ormond Street Hospital for Children NHS Foundation Trust, London, WC1N 3JH, UK <sup>27</sup>Department of Pediatrics, The Medical University of Warsaw, wirki i Wigury 61, 00-001 Warszawa, Poland <sup>28</sup>South West Thames Regional Genetics Service and St George's University of London and Institute of Cancer Research, London, SW17 0RE, UK <sup>29</sup>Regional Center for CLP, Smile-House, San Paolo University Hospital, Via Antonio di Rudini, 8, 20142, Milan, Italy <sup>30</sup>Kennedy Center, Department of Clinical Genetics, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark <sup>31</sup>Department of Pediatrics, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam-Zuidoost, Amsterdam, Netherlands <sup>32</sup>Center for Pediatrics and Adolescent Medicine, Johannes Gutenberg University Medical Center, Langenbeckstr. 1, D-55101, Mainz, Germany <sup>33</sup>Institute of Human Genetics, University Hospital, Technical University of Aachen, Templergraben 55, 52062, Aachen, Germany <sup>34</sup>Human Development and Health, Faculty of Medicine, University of Southampton, Southampton SO17 1BJ, UK <sup>35</sup>DiSTABiF, University of Campania Luigi Vanvitelli, Caserta and Institute of Genetics and Biophysics "A. Buzzati-Traverso" - CNR, Via Pietro Castellino,

111,80131, Naples, Italy <sup>36</sup>Department of Medical Genetics, University of Cambridge and NIHR Cambridge Biomedical Research Centre and Cancer Research UK Cambridge Centre, Cambridge Biomedical Campus, Cambridge, CB2 0QQ, UK

## Abstract

Beckwith–Wiedemann syndrome (BWS), a human genomic imprinting disorder is characterised by phenotypic variability that might include overgrowth, macroglossia, abdominal wall defects, neonatal hypoglycaemia, lateralised overgrowth and predisposition to embryonal tumours. Delineation of the molecular defects within the imprinted 11p15.5 region can predict familial recurrence risks and the risk (and type) of embryonal tumour. Despite recent advances in knowledge, there is marked heterogeneity in clinical diagnostic criteria and care. As detailed in this Consensus Statement, an international consensus group agreed 72 recommendations for the clinical and molecular diagnosis and management of BWS, including comprehensive protocols for the molecular investigation, care and treatment from the prenatal period to adulthood. The consensus recommendations apply to patients with Beckwith–Wiedemann spectrum (BWSp) covering classical BWS without a molecular diagnosis and BWS-related phenotypes with an 11p15.5 molecular anomaly. Although the consensus group recommend a tumour surveillance programme targeted by molecular subgroups, surveillance might differ according to the local healthcare system (for example, in the United States), and the results of targeted and universal surveillance should be evaluated prospectively. International collaboration, including prospective audit of the results of implementing these consensus recommendations, is required to expand the evidence base for the design of optimum care pathways.

## Table of Contents Blurb

Beckwith–Wiedemann syndrome is an overgrowth disorder characterized by variable clinical phenotypes and a complex molecular aetiology. This Consensus Statement summarises recommendations for clinical indications, molecular diagnosis and management of the newly defined Beckwith–Wiedemann spectrum.

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## Introduction

Beckwith–Wiedemann syndrome (BWS) is a multisystem human genomic imprinting disorder with variable clinical expression and complex molecular aetiology<sup>1</sup>. BWS is an overgrowth syndrome, with patients often presenting with macroglossia, abdominal wall defects, hemihyperplasia, enlarged abdominal organs, and an increased risk of embryonal tumours during early childhood. BWS is mainly due to genetic or epigenetic defects within the 11p15.5 region. This region contains imprinted genes such as *CDKN1C* or *IGF2*, which are strong regulators of foetal growth. Although BWS might present prenatally or in adult life, it is most commonly diagnosed in the neonatal period or in early childhood with an estimated prevalence of 1 case per 10,340 live births<sup>2</sup>. Since the first descriptions half a century ago, a PubMed search conducted on 15th Nov 2017 for “Beckwith Wiedemann”, “Wiedemann Beckwith” or “EMG syndrome” yielded more than 1,500 BWS-related

articles. However, there is variable clinical practice regarding the diagnosis and care of individuals with BWS.

To address these issues, the European Cooperation in Science & Technology (COST)-funded European Network for Congenital Imprinting Disorders initiated a BWS Consensus Programme that involved an extensive literature review, preparation and critical appraisal of draft documents and a final face-to-face consensus meeting involving invited experts and patient group representatives. This effort produced a series of consensus recommendations for the diagnosis and care of individuals with the newly defined Beckwith–Wiedemann spectrum (BWSp), which are presented in this Consensus Statement.

## Methods

A PubMed search (key words: “Beckwith Wiedemann”, “Wiedemann Beckwith” or “EMG syndrome”) yielded more than 1,500 articles. Articles of interest were selected based on the abstracts, considering especially the number of patients included and the description of the molecular mechanisms. Only articles mentioning the molecular mechanisms have been retained. Articles have then reviewed by at least two experts and sorted out into three groups: clinical diagnosis (group 1), molecular diagnosis (group 2) and clinical management (group 3)

The International BWS Consensus Group comprised 41 participants from 36 institutions across 11 countries, predominantly based in Europe, including clinicians, clinical and research scientists and patient group representatives with expertise in different aspects of BWS (clinical and molecular geneticists, paediatric endocrinologists, oncologists, orthopaedists, oro-facial surgeons and nephrologists).. A modified Delphi consensus process was adopted<sup>3</sup>. Discussions took place via conference calls, email communications and file exchanges. Two face-to-face meetings were held; a preliminary meeting of 11 participants (including one patient group representative) in February 2016 to identify the key issues to be addressed by the consensus group, and a plenary 3-day meeting involving 35 participants (including two patient group representatives) in March 2017. During this plenary meeting, experts participated in one of the three subgroups (clinical/molecular/management), based on their field of expertise, discussed the draft consensus documents, formulated and voted on the consensus recommendations (BOX 1). This Consensus Statement summarises the outcome of these discussions and is divided into three subject areas; clinical aspects, molecular aspects and care and management.

### Box 1

#### Details of the consensus voting process

For voting on individual recommendations, participants (n=33) selected from the following options (patient group representatives did not vote)

- A. Evidence or general agreement allow full agreement with the recommendation
- B. Evidence or general agreement are in favour of the recommendation

- C.** Evidence or general agreement are weak for the recommendation
- D.** There is not enough evidence or general agreement to agree with the recommendation

Depending on the proportion of votes received, the strength of the recommendation was recorded as follows:

- + 26–49% of the votes
- ++ 50–69% of the votes
- +++ 70% of the votes

## Clinical aspects of BWS

Since the seminal descriptions by Beckwith<sup>4</sup> and Wiedemann<sup>5</sup> in the 1960s, there have been many attempts to define BWS using various clinical criteria that have been reported with different prevalences in cohorts of BWS (Supplemental Table 1); however, no agreed clinical definition of BWS has emerged. Since the findings in the 1990s of molecular abnormalities of chromosome 11p15.5 in BWS<sup>6–8</sup>, it has been recognised that these genetic and epigenetic changes are frequently mosaic and lead to a range of clinical phenotypes. These include ‘classical BWS’ (OMIM #130650), which is characterised by macroglossia, anterior abdominal wall defects and prenatal and postnatal overgrowth, among others (Supplementary Table 1), and also some cases of isolated lateralised overgrowth (previously called ‘isolated hemihypertrophy’ or ‘isolated hemihyperplasia’; OMIM #235000)<sup>9</sup> and patients with a chromosome 11p15.5 molecular anomaly who do not fit into these first two groups, a condition termed ‘atypical BWS’ by this consensus. Given the overlapping phenotypes and common molecular mechanisms between these groups, the Consensus Group decided that these phenotype and/or genotype combinations could be best classified as parts of the BWSp (**R1**, TABLE 4) and that the recommendations of this consensus should be applied to individuals with BWSp (FIG. 1; TABLE 4).

## Clinical features of BWSp

BWS has classically been characterized by macroglossia, macrosomia, abdominal wall defects and an increased risk for embryonal tumours<sup>10–16</sup>. There is growing recognition that not all patients with BWS display all of these phenotypic features and that patients have remained undiagnosed because they did not present with one of these features, such as macrosomia which was initially considered as a cardinal feature but is present in only half of the patients with an 11p15.5 molecular defect<sup>17,18</sup>. The clinical features outlined as part of the consensus BWSp scoring system include features that, when present, are more likely to lead to a positive diagnosis (termed ‘Cardinal features’), including macroglossia, exomphalos, lateralized overgrowth, multifocal Wilms tumour or nephroblastomatosis, hyperinsulinism and specific pathology findings (such as adrenal cytomegaly or placental mesenchymal dysplasia, table 1). Macrosomia has been defined according to different criteria in different clinical cohorts<sup>10–12,14–16</sup>, making it challenging to assess the role it has as a cardinal feature. Lateralized overgrowth is the novel term for hemihypertrophy (or

hemihyperplasia), which is defined as asymmetric overgrowth of part of the body<sup>9</sup>. Embryonal tumours such as Wilms tumours and hepatoblastoma can occur outside of the diagnostic scope of BWSp; however, multifocal Wilms tumours are more likely to occur in BWSp. As a cardinal feature, hyperinsulinism is defined as prolonged hypoglycaemia in the context of elevated insulin levels that last beyond one week and/or require escalated treatment<sup>19</sup>, while transient hypoglycaemia resolving without the need for further intervention. Although pathology findings cannot always be evaluated (especially when BWSp is not suspected prenatally or at birth, and when placental samples are not collected), the diagnosis of BWSp should be considered in cases of adrenal cortex cytomegaly, placental mesenchymal dysplasia and pancreatic adenomatosis<sup>4</sup>. Additionally, if samples are available (especially from the placenta after birth) and the diagnosis is being considered, pathological investigation can be beneficial in making the clinical diagnosis.

Features characterized as ‘Suggestive Features’ are likely to occur independently in the general paediatric population and are therefore given less weight in the consensus BWSp scoring system outlined in the next section. Suggestive features include a birth weight greater >2 standard deviations score (SDS), facial naevus flammeus, polyhydramnios or placentomegaly, ear creases or pits, transient hypoglycaemia, embryonal tumours, nephromegaly or hepatomegaly and umbilical hernias or diastasis recti.

### Consensus scoring system and definition

The many previously proposed systems to define BWS have suggested various combinations of clinical features (with macroglossia, exomphalos and/or (asymmetric) overgrowth as major features)<sup>10–12,17,20,21</sup> with the aim of optimizing the likelihood of a classical and molecularly confirmed diagnosis. Frequently cited and recent phenotype articles from the last 25 years were reviewed for the prevalence of individual clinical features (Supplementary Table 1), which were then classified as cardinal or suggestive features (TABLE 1). As several of these articles referenced the same patient cohorts<sup>11–15,17,20–25</sup>, data was analysed from the nine articles describing apparently distinct cohorts<sup>10,11,13,14,17,20,22,24,25</sup>. The goal of this BWSp scoring system (TABLE 1; TABLE 4 was to recognise that BWS falls into a clinical spectrum and that some features that have long considered to be classical parts of the syndrome are not present in every patient, and therefore the diagnosis should not be dismissed due to the absence of such features. Additionally, this consensus statement sought to include elements that could be pathognomonic for BWS. In addition to informing the presence of a diagnosis of classical BWS, the consensus group also determined that the same system could be used to provide guidance regarding when to pursue genetic testing. We compared this new scoring system with previously published systems (Supplementary FIG. 1), keeping in mind that previous systems focused on the diagnosis of classical BWS and molecularly confirmed BWS, and not the diagnosis of the BWSp.

Cardinal features are considered key to the clinical diagnosis, whereas suggestive features add to the likelihood of a clinical diagnosis and the indications for molecular testing, but are less specific (TABLE 1). Cardinal and suggestive feature designations were analysed in the BWSp cohort reported by Ibrahim *et al.*<sup>10</sup> and were shown to be largely superior to previous diagnostic systems (Supplementary FIG. 1). A limitation was that transient hypoglycaemia

versus prolonged hyperinsulinism were not typically distinguished in the prior cohorts, so this feature could therefore not be assessed, and that macrosomia was variably defined in previous cohorts<sup>10–13,16,17,20,21</sup>

Cardinal features include macroglossia, exomphalos, lateralized overgrowth, multifocal Wilms tumour, prolonged hyperinsulinism and distinct pathologic findings that are unique to BWS. The major differences between the consensus and previous scoring systems are the classification of macrosomia and hyperinsulinism. Although it is often associated with BWSp, macrosomia (defined as height and/or weight >2 SDS) is no longer considered a cardinal feature as it is variably defined in previous cohorts and it might only be present in about half of patients with BWS<sup>15,25</sup>. Hyperinsulinism (defined in **R5**, TABLE 4) without another identifiable molecular cause can be the initial presenting feature of BWSp<sup>26,27</sup>. Hyperinsulinism is classified as a cardinal feature when lasting beyond one week and requiring escalated treatment, and as a suggestive feature when lasting less than a week.

For simplicity and consistency, we have developed consensus criteria using cardinal and suggestive features (TABLE 1; R2, TABLE 4). For a clinical diagnosis of classical BWS, a patient requires a score of  $\geq 4$  based on cardinal and suggestive features; this clinical diagnosis does not require the molecular confirmation of an 11p15.5 anomaly. Patients with a score of  $\geq 2$  (including those with classical BWS with a score of  $\geq 4$ ) merit genetic testing according to our algorithm for investigation and diagnosis of BWS (FIG. 3). Patients with a score of  $< 2$  do not meet the criteria for genetic testing. Patients with a score of  $\geq 2$  with negative genetic testing should be considered for an alternative diagnosis and/or referral to a BWS expert for further evaluation.

Clinical diagnosis within the BWSp beyond the clear diagnosis of classical BWS or a clear molecular diagnosis is challenging and requires a combination of molecular testing and physician opinion. There is currently not enough published data to provide clear clinical recommendations for patients with a score of  $< 4$  who have no molecular abnormality. Nonetheless, patients with a cardinal feature of BWS (such as macroglossia, hyperinsulinism, a multifocal Wilms tumour or a pathological finding) should be referred to a specialist with expertise in BWS for further evaluation. Patients with isolated exomphalos are more common and are less likely to have an 11p15.5 defect compared to patients with other isolated symptoms and should therefore not be included in the BWSp. Lateralized overgrowth can occur both as a symptom of BWSp and independent of BWSp<sup>9</sup>. When lateralized overgrowth occurs with an 11p15 abnormality, it is considered part of BWSp. As there are multiple molecular causes of lateralized overgrowth aside from 11p anomalies (e.g. *PIK3CA*, *AKT1* mutations), lateralized overgrowth without an 11p15 anomaly in a child who does not meet the criteria for classical BWS was considered to be outside the BWSp and the scope of this consensus statement; thus, recommendations for further investigation and clinical management were not made (**R3**, TABLE 4).

### Indications for molecular testing

The consensus group recommended that molecular testing is indicated in cases with a score of  $\geq 2$  (TABLE 1), unless there is an alternative explanation (for example, gestational diabetes mellitus for macrosomia) (**R4**, TABLE 4). For isolated exomphalos, molecular



testing is discretionary. Testing is recommended in patients with a family history and a known heritable pathogenic 11p15 anomaly (a positive family history might occur in 10–15% of patients<sup>28,29</sup>). Some features included in some previous diagnostic criteria (for example, cleft palate, advanced bone age, polydactyly and supernumerary nipples) are suggestive of an alternative diagnosis such as Simpson–Golabi–Behmel syndrome<sup>30</sup> and are therefore not included in the consensus scoring system. Although renal abnormalities are common in patients with BWSp, they are usually present with other features and not as an isolated feature. When molecular testing is negative, other relevant disorders should be considered in the differential diagnosis (FIG. 3; Supplementary Table 2).

### Assisted reproduction technology

Assisted reproductive technologies (ART) are defined as treatments handling male and female gametes outside of the body, and include procedures such as *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI)<sup>31</sup>. ART account for 1–3% of all births in industrialized countries<sup>31</sup>. Although these techniques are regarded as safe, it has been suggested that the establishment and/or maintenance of DNA methylation at imprinted loci might be disturbed by ART<sup>31–36</sup>. Following reports of children with a rare molecular subtype of Angelman syndrome who were conceived by ICSI<sup>32,33</sup>, and an increased frequency (~4–6-fold) of ART births in children with BWS<sup>34–36</sup>, a population-based study estimated the risk of BWS in IVF-conceived children to be ~1 in 4,000, substantially greater than in the general population<sup>31</sup>. A study from 2017 reported a 10-fold increased risk of BWS with ART, but an absolute risk of ~1 in 1000<sup>37</sup>. Although some epidemiological studies have not detected an increased relative risk of BWS in children born after ART<sup>38,39</sup>, molecular studies support an association as >90% of children with BWS conceived by ART have an epimutation at the centromeric imprinting centre *KCNQ1OT1*:TSS DMR (IC2), compared to ~50% of children with BWS who were not conceived by ART<sup>40</sup>. Various factors might contribute to an association between ART and Angelman syndrome or BWS, including infertility *per se* (i.e. independently to ART techniques)<sup>41,42</sup>, superovulation or *in vitro* embryo culture<sup>43–45</sup>. The link between ART and epigenetic defects has also been suggested by the large offspring syndrome (an ART-associated phenomenon in sheep and cows that has some phenotypic similarity to BWS) which has been reported to be associated with epigenetic alterations similar to those observed in BWS<sup>46</sup>. However, although there is clear evidence linking ART and BWS, additional research is required to further elucidate the relationships between subfertility, hormonal stimulation, embryo manipulation and imprinting defects (TABLE 4; R6).

### Molecular aspects of BWSp

BWSp is associated with molecular abnormalities affecting a cluster of imprinted genes located within the chromosome region 11p15.5–11p15.4 and divided in two functionally independent domains, the centromeric and telomeric domains (FIG. 2)<sup>28</sup>. Each domain harbours its own imprinting control region, marked by a differentially methylated region (DMR). The insulin-like growth factor 2 encoding gene *IGF2* and the gene encoding the non-translated long non-coding RNA (lncRNA) *H19* are located in the telomeric domain and are controlled by the *H19/IGF2*:IG DMR (*H19/IGF2* intergenic DMR), also known as

imprinting control region 1 (ICR1), *H19*-DMR or Imprinting Centre 1 (IC1); OMIM \*616186. The cell cycle inhibitor gene *CDKN1C* and the gene encoding the regulatory long non-coding RNA *KCNQ1OT1* are located in the centromeric domain and are controlled by the *KCNQ1OT1*:TSS DMR (*KCNQ1OT1* transcriptional start site DMR, also known as KvDMR, *LIT1*-DMR, imprinting control region 2 (ICR2) or Imprinting Centre 2 (IC2); OMIM \*604115). The Human Genome Variation Society (HGVS)-recommended nomenclature, *H19/IGF2*:IG DMR and *KCNQ1OT1*:TSS DMR, should be adopted in publications and test reporting<sup>47</sup> (**R7**, TABLE 5); however, for brevity, IC1 and IC2 are used hereafter.

A molecular defect affecting imprinted genes in chromosome region 11p15 can be demonstrated in ~80% of patients with BWS<sup>26</sup>. DNA methylation abnormalities are the most frequent defects; loss of methylation (LOM) at the maternal IC2 allele is found in ~50% of patients and gain of methylation (GOM) at the maternal IC1 allele in 5–10% of cases<sup>48</sup>. Mosaic segmental paternal uniparental isodisomy (UPD) of 11p15.5 (commonly referred to as segmental upd(11)pat) can be detected in 20% of patients, intragenic *CDKN1C* mutations in 5% of sporadic and 40% of familial cases, and chromosomal abnormalities in 11p15 in <5% of patients and a molecular diagnosis is not reached in up to 20% of patients<sup>28</sup>. The frequency of twinning is markedly higher in patients with BWS than the general population; in the majority of cases, twins are female, monozygous and discordant (that is, one twin is affected and one is unaffected by BWS)<sup>49</sup>. Due to the sharing of circulation during development, DNA from blood cells or saliva might show aberrant DNA methylation (usually IC2 LOM) in both affected and unaffected discordant twins, whereas methylation is concordant with phenotype in non-blood-derived samples such as buccal swab<sup>50</sup>. Thus, buccal swab is the preferred source of DNA for unambiguous diagnosis in cases of discordant monozygotic twins.

### Molecular genetic testing for BWS

A flowchart summarising the molecular diagnostic pathway for investigation of suspected BWS is presented in FIGURE 3 (TABLE 5; R8).

First line molecular testing procedures should assay IC1 and IC2 methylation (TABLE 5, R9). Methylation is abnormal in cases of IC2 LOM, IC1 GOM, copy number variations (CNVs) and segmental upd(11)pat (both IC2 LOM and IC1 GOM)<sup>51</sup>. Abnormal methylation status confirms a diagnosis of BWS, but its underlying mechanism must be established to define management, genetic counselling and recurrence risks<sup>48,51</sup>. Thus, if methylation is assayed using a technique that does not estimate DMR copy number, this should then be determined in all cases with IC1 and/or IC2 methylation abnormalities (FIG. 3). Currently, methylation-specific (MS) multiplex ligation-dependent probe amplification (MS-MLPA) is the most common diagnostic test, as it simultaneously detects DMR methylation status and copy number; however, other techniques (such as MS-PCR and MS-qPCR) are more sensitive in cases with low-level mosaicism (for a detailed list, see references<sup>51–54</sup>).

**Recommended investigations if testing for methylation abnormalities is positive**—If a DMR CNV is implied using a PCR-based methodology (such as MS-

MLPA), chromosome microarray analysis (such as oligonucleotide polymorphism-based or single nucleotide polymorphism (SNP)-based arrays should be considered to determine the nature and extent of the deletion or duplication, and karyotyping, fluorescence *in situ* hybridization (FISH), or subtelomeric MLPA should be considered to identify possible chromosomal translocations<sup>54–57</sup>. Testing can then be extended to other family members as appropriate. A SNP-based array will also allow detection of uniparental disomy (and indeed mosaicism) if a CNV is not detected.

If IC1 GOM and IC2 LOM are detected without evidence of CNV, mosaic segmental upd(11)pat is probable and can, if necessary, be confirmed using microsatellite analysis or SNP-based chromosome microarray analysis<sup>58–61</sup> SNP-based chromosome microarray is considered to be the most sensitive method to investigate low mosaic (for example, 1–5%) segmental upd(11)pat<sup>59</sup>. Mosaic paternal unidiploidy (that is, genome-wide paternal upd affects up to 10% of cases with uniparental disomy and, as mosaic paternal unidiploidy is associated with additional clinical features and an increased risk of tumour development, further investigations (SNP array or microsatellite analysis) to detect this molecular abnormality should be considered<sup>62–67</sup> (TABLE 5, R10).

Up to 20% of patients with IC1 GOM might carry small CNVs in the DMR which cannot be detected using chromosome microarray analysis, or single nucleotide variations (SNVs) in octamer-binding protein 4 (OCT4) or SOX binding sites; these CNVs and SNVs are associated with a high risk of recurrence<sup>68–74</sup>. Although some small CNVs can be detected using MS-MLPA, detection of SNVs would require additional investigations that are unavailable in most diagnostic laboratories (TABLE 5, R11). However, targeted IC1 sequencing can be considered in a specialised laboratory if MS-MLPA shows IC1 GOM and no CNV, especially if there is a family history of BWSp.

IC2 LOM is the most common epigenetic finding in BWSp but IC2 DMR deletions are rare<sup>55</sup>, and at present there is no indication for analysing patients with BWSp and IC2 LOM for SNVs. Approximately one third of patients with IC2 LOM have multi-locus imprinting disturbance (MLID)<sup>75–78</sup>. In most patients, the clinical significance of MLID is uncertain and therefore routine testing for MLID is not usually indicated; however, in cases with IC2 LOM and a family history of BWSp and no IC2 DMR CNV, MLID testing might help to determine if further testing for *transacting* mutations should be considered<sup>79,80</sup>

**Recommended investigations if first-line molecular testing is negative—**A negative result for first-line molecular testing for IC1 and IC2 methylation does not exclude BWSp for a variety of reasons, including low-level mosaicism that is below the limit of detection of methylation testing; a *CDKN1C* mutation; a rare balanced chromosomal rearrangement (for example, inversion and/or translocation); an unrecognised or undetected cause of BWSp (~20% of patients with a characteristic BWS phenotype remain without a molecular diagnosis<sup>28</sup>); or an incorrect clinical diagnosis (TABLE 5, R12–R15). Further molecular testing should be prioritised according to the most probable cause; for example, a less severe phenotype with lateralized overgrowth would suggest mosaicism, whereas a classical BWS phenotype with an abdominal wall defect and a positive family history would indicate a potential *CDKN1C* mutation.

Mosaicism for the molecular defect occurs in most sporadic cases of BWSp, and different tissues might have different proportions of affected cells<sup>81</sup>. First-line diagnostic testing is usually performed using blood-leukocyte DNA, and IC1 or IC2 methylation level might be equivocal or within the normal range. Analysis of DNA from buccal swabs, cultures of fibroblasts or cells of mesenchymal origin (for example, obtained at the from surgical resection/excision of hyperplastic tissues ) improves the detection rate for all mosaic defects<sup>51,54,81</sup> (TABLE 5, R13).

*CDKN1C* mutations account for ~5% of sporadic cases of BWS and for 40% of familial cases (in the case of maternal inheritance)<sup>48,82</sup>. Detection of a candidate pathogenic *CDKN1C* variant enables appropriate cascade testing to clarify familial recurrence risks<sup>82,83</sup>. Rare cases of apparently *de novo CDKN1C* mutations can arise in siblings, presumably resulting from maternal germline mosaicism<sup>83</sup>.

Rare maternally inherited balanced translocations or inversions involving chromosome region 11p15 might or might not be associated with IC2 methylation anomalies, and should be considered if first-line testing is negative<sup>84–87</sup> (TABLE 5, R14). Finally, when molecular testing is negative, other relevant disorders should be considered as differential diagnoses (FIG. 3; Supplementary Table 2, R15).

### Multi-locus imprinting disturbance

Multi-locus imprinting disturbances (MLID) are those with altered DNA methylation in addition to the lesion responsible for the primary clinical presentation<sup>88</sup>. MLID has a higher prevalence in BWSp than in other imprinting disorders, and genome-wide analyses have revealed MLID in approximately one third of patients with BWSp who have IC2 LOM, but not in patients with segmental upd(11)pat or IC1 GOM<sup>48,75–78,81,88–91</sup>. In BWSp, MLID almost exclusively involves loci methylated in the maternal, and not the paternal, germline, although rare cases show LOM at both IC2 and IC1 (the latter finding is a feature of the growth restriction disorder Silver–Russell syndrome (SRS))<sup>76,92</sup>

Rare cases of BWSp-MLID have been associated with biallelic maternal-effect genetic mutations in *NLRP2*<sup>79</sup> and *NLRP5*<sup>80</sup> (which encode NACHT, LRR and PYD domains-containing protein 2 (NLRP2) and NLRP5), and therefore the possibility of an underlying *trans*-acting genetic mutation in these genes may warrant consideration in genetic counselling.

Perhaps owing to the variable methylation alterations and frequent mosaicism seen in MLID, its effect on the BWS clinical phenotype remains unclear<sup>75,76,78,89,92,93</sup> and therefore routine clinical diagnostic testing is not a recommendation of this consensus.

### Recurrence risks in BWSp

The recurrence risk for BWSp depends on the genetic aetiology and nature of any genetic or epigenetic defect identified, as well as its parental origin, and therefore it is recommended that family counselling should be performed by an individual experienced in the field of imprinting disorders, and should take into account the precise nature of the anomaly detected (TABLE 5, R16, R17). It has been reported that up to 10–15% of cases of BWSp

are familial and most commonly result from *CDKN1C* mutations, chromosome 11p15 abnormalities and genetic alterations within IC1<sup>28,29</sup>. In these cases, the mode of inheritance is autosomal dominant, but the recurrence risk is dependent on the sex of the parent transmitting the affected allele (TABLE 2) (TABLE 5, R17).

Pathogenic *CDKN1C* variations have a 50% recurrence risk with variable expressivity if the mutation is inherited from the mother<sup>82,83</sup>. In principle, all 11p15 CNVs and balanced translocations have a 50% recurrence risk with parent-of-origin-dependent phenotypes<sup>54,84,86,87</sup>. In cases with paternal duplication of 11p15 resulting from the unbalanced segregation of a translocation or an inversion individuals carrying the balanced rearrangement have a normal phenotype<sup>94</sup>. In some pedigrees, either BWS or SRS has been observed depending upon paternal or maternal transmission of the 11p15 duplication<sup>57,95,96</sup>. Paternal transmission of a duplicated telomeric domain and maternal transmission of a deleted centromeric domain also usually result in BWSp with a high recurrence risk<sup>52,95,97,98</sup>. Prediction of phenotype and recurrence risks that are associated with smaller CNVs within either the telomeric or centromeric domain can be complex, as it depends on their size and the genes and regulatory elements involved<sup>55,99–104</sup>.

Internal IC1 CNVs and SNVs have recurrence risk as high as 50% when occurring on the maternal allele, although incomplete penetrance and possible anticipation has been observed in some cases<sup>73,105,106</sup>. Rare familial cases of BWSp-MLID might be caused by maternal effect gene mutations (for example, *NLRP2* or *NLRP5* mutations) and might be associated with a very high recurrence risk<sup>79,80</sup>. In the cases that harbour other molecular defects, the recurrence risk is generally low (TABLE 2).

### Prenatal molecular diagnosis

Prenatal testing for BWS poses particular challenges since, in addition to general aspects of molecular testing (such as the range of molecular disturbances, the challenge of mosaicism detection and the technical limitations of testing), the reliability and informative value of prenatal test results and the ethical issues involved must be considered prior to sampling<sup>107</sup>.

The major indications for prenatal diagnosis of BWSp are familial cases with a known genetic alteration and a high recurrence risk and cases with no family history in which possible features of BWSp (usually exomphalos, but also macrosomia, hemihypertrophy, organomegaly and polyhydramnios) have been detected using prenatal foetal ultrasonography (TABLE 5, R18). The diagnostic testing for prenatal samples does not therefore necessarily follow the same flow as that for postnatal samples, but reflects the individual situation (TABLE 5, R19).

Although chorionic villus (CVS) cells, amniotic fluid (AF) cells or foetal blood cells (native and cultured) might be used for molecular testing, it is possible that cell culture might influence the methylation patterns<sup>108</sup>. In CVS cells, the methylation pattern at 11p15.5 might be different from that of embryonic tissues<sup>108</sup> and/or CVS cells might not reflect the (epi)genetic constitution of the foetus, and therefore false positive results might occur<sup>107</sup>. False-negative prenatal tests might occur with all types of testing due to mosaicism; therefore, a normal prenatal test result cannot absolutely exclude a diagnosis of BWSp

(TABLE 5, R20). Because of the relatively recent adoption of prenatal testing, and the challenges involved, it is recommended that multi-centre audit of cases, methods and diagnostic rates be implemented prospectively, to enable ongoing refinement of best practice guidelines (TABLE 5, R21)

## Care and management aspects of BWSp

In view of the complex multisystem manifestations of BWSp, the consensus group recognised the requirement for effective coordination of healthcare (TABLE 6, R22).

### Prenatal management

In cases of BWSp for which a risk of recurrence has been identified (TABLE 2), some parents might wish to consider prenatal diagnosis. If a molecular diagnosis is not available or indicated, then ultrasonographic detection of an anterior abdominal wall defect, macroglossia or, less specifically, macrosomia, visceromegaly, polyhydramnios, placentomegaly or pancreatic overgrowth, might indicate a likely diagnosis of BWSp<sup>109</sup>. Rarer manifestations detectable by prenatal ultrasound scan (USS) include placental mesenchymal dysplasia, urinary tract abnormalities, cardiac defects, adrenal cysts and masses<sup>110,111</sup>. Abnormal prenatal biochemical screening results — for example, elevated levels of free beta-human chorionic gonadotropin (hCG) in the first trimester<sup>109–111</sup> and/or increased  $\alpha$ -fetoprotein ( $\alpha$ FP) levels in the second trimester (associated with exomphalos)<sup>112</sup> — can be associated with BWSp in the foetus. In pregnancies known to be at increased risk of BWSp, the presence of a single anomaly (for example, exomphalos) might be sufficient to make a presumptive diagnosis.

In pregnancies without a previous history of BWSp, none of the prenatally detectable features of BWSp are, in isolation, pathognomonic. Approximately 10–20% of foetuses with a prenatally diagnosed isolated exomphalos<sup>112,113</sup>, and ~20% of those with placental mesenchymal dysplasia<sup>114</sup>, will have BWSp. As cytogenetic and/or chromosome microarray analysis is indicated for both of these findings, molecular analysis for BWSp can also be performed on the same sample, and confirmation or exclusion of BWSp might be helpful for the parents. For less specific features (for example, urinary tract abnormalities and cardiac defects) testing for BWSp is likely to depend on whether there are multiple BWSp-related features present.

When a prenatal diagnosis of BWSp is suspected or confirmed, the management of individual congenital anomalies (for example, exomphalos or cardiac defect) generally follows standard protocols, based on usual local practices. However, macrosomia might cause problems (for example, shoulder dystocia) at delivery, and therefore growth should be carefully monitored in the latter stages of pregnancy and appropriate arrangements for delivery should be made (TABLE 6, R23 and R24). BWSp is also associated with polyhydramnios and premature birth. Potential post-delivery complications such as neonatal hypoglycaemia, respiratory obstruction from macroglossia, surgical repair of exomphalos, and so on, should be anticipated and appropriate monitoring and facilities put in place.

Maternal complications associated with a diagnosis of foetal BWSp include gestational hypertension (~2.4-fold increased risk [ ]) and pre-eclampsia<sup>115,116</sup>. In addition, HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome has been reported occasionally in BWSp<sup>116,117</sup>. Therefore, in case of a suspicion of foetal BWS, such a condition should be looked for with a lower threshold compared with normal pregnancies.

### Growth and lateralised overgrowth

Although prenatal and postnatal overgrowth have been considered to be cardinal features in previous reports, overgrowth occurs in only 43–65% of patients<sup>118</sup>. Overgrowth at birth might be relatively more common in patients with IC1 GOM and segmental pat(11)upd than in other molecular subgroups<sup>13,16</sup>. Postnatal growth is generally in the upper part of the normal range, but usually slows in late childhood, and differences in growth trajectories between children with BWSp and those without should be considered when making predictions of adult height. However, growth trajectories have not been well reported in patients with BWSp, and specific growth charts are needed (Table 6, R25). Although few data on final adult height is available, one study reported that final adult height was higher than parental target height with a mean distance to target height of  $1.7 \pm 1.1$  SDS, with about half of the patients  $>2$  SDS<sup>14</sup> (TABLE 6, R26). Advanced bone age is infrequent (~3%)<sup>119,120</sup> and, to date, there is no data regarding treatment of tall stature in cohorts of patients with BWSp (TABLE 6, R27).

Lateralised overgrowth might occur in all molecular subtypes of BWS, but it is rare in patients with a *CDKN1C* mutation and is the most frequent feature in patients with segmental upd(11)pat<sup>10,13</sup>. Molecular abnormalities in region 11p15 might be observed in patients with isolated lateralised overgrowth, which enables a diagnosis of BWSp in such cases<sup>119,121</sup>. Leg length discrepancy (LLD) can be associated with significant morbidity and negatively influence quality of life<sup>122</sup>. The management of LLD will depend on severity (TABLE 6, R28-R31). Shoe-lifts might be indicated for LLD  $< 2$ cm. As in isolated (non-BWSp) LLD, epiphysiodesis might be considered for LLD discrepancy  $>2$ cm<sup>123</sup> (TABLE 6, R30). Surgical correction of upper limbs asymmetric overgrowth is generally not indicated (TABLE 6, R32).

### Management of macroglossia

90% of children diagnosed with classical BWS have macroglossia, and BWSp is the most common cause of macroglossia in childhood<sup>124</sup>. Although macroglossia might appear to regress spontaneously in some children (from a combination of a decrease in growth velocity and an increase in growth of the mandible), ~40% undergo a surgical tongue reduction<sup>125</sup>. The most common indications for surgery are problems with feeding; persistent drooling; difficulties with articulation; orthodontic problems, including prognathism and development of an anterior open-bite and incisor spacing/flaring; and psychosocial difficulties resulting from abnormal cosmetic appearance and difficulties with speech, feeding and drooling<sup>126–128</sup> (TABLE 6, R33–35).

The enlarged tongue is usually increased in size in all three dimensions and the aim of surgery is to reduce the tongue bulk while preserving normal shape and improving function.

The most common surgical approach is anterior wedge resection but a variety of other techniques have been described<sup>125,128,129</sup>. Surgical complications, although infrequent, can include postoperative oedema of the tongue and wound dehiscence.

In rare cases, respiratory problems might require surgery to be performed in the neonatal period and preoperative tracheostomy might be required<sup>125</sup>. When obstructive sleep apnoea is suspected, an airway evaluation and appropriate further investigation with polysomnography can be used for objective assessment<sup>130,131</sup> (TABLE 6, R33). In the absence of respiratory obstruction, surgery is generally delayed until at least age 12 months (when tongue size is more stable) (TABLE 6, R34–34). If the indication for surgery is unclear, the child's progress should be monitored to determine if indications arise in the future. Long-term follow-up studies generally show favourable results of surgery in most cases with cosmetic improvement, reduced drooling, resolution of feeding difficulties, improved speech, adequate tongue mobility and, usually, no substantial effect on taste sensation<sup>126–128</sup>. Surgery has been reported to provide good outcomes in children who are operated on at a wide variety of ages, but mainly before 2–3 years<sup>125,127</sup>.

To facilitate objective assessments and accrual of accurate long-term prognostic data, surgery should, whenever possible, be restricted to a small number of units that can offer a multidisciplinary service (including an experienced surgical team) and long-term follow up (TABLE 6, R35–R38).

### Management of exomphalos

Exomphalos is a cardinal feature of BWSp (TABLE 1) and is preferentially associated with molecular defects occurring within the centromeric domain (IC2 LOM or *CDKN1C* mutations)<sup>10,13,16</sup>. To date, no specific recommendations have been given regarding the management of exomphalos occurring in patients with BWSp compared with isolated exomphalos in accordance with usual local practices (TABLE 6, R39).

Molecular investigations of apparently isolated exomphalos in neonates rarely detect a molecular abnormality in the absence of additional BWS features<sup>132</sup>.

### Management of hypoglycaemia

Hypoglycaemia in BWSp is due to excess insulin and occurs in 30–60% of children with BWSp<sup>10,13,16</sup>. Although BWSp-related neonatal hypoglycaemia is often transient and resolves within a few days, in up to 20% of neonates it can persist beyond the first week of life and require medical treatments or even pancreatectomy in the most severe cases<sup>19</sup>.

Congenital hyperinsulinism is a rare condition with a range of causes<sup>19,133</sup>. In a cohort of 501 patients with hyperinsulinism (excluding patients with focal hyperinsulinism), ~6% had features of BWSp (most of whom had segmental upd(11)pat) and half of these patients underwent surgery due to persistent hypoglycaemia after optimal medication<sup>26</sup>.

Although low plasma glucose concentrations are common during the first 24 hours of life in all newborns, by day 3 plasma, plasma glucose concentrations in neonates are similar to those of older children, with a normal range of 3.5–5.5 mmol/l (60–100 mg/dL)<sup>134</sup>. A



diagnosis of hyperinsulinism is based on evidence of increased insulin secretion and/or actions at the time of hypoglycaemia, including a detectable insulin level, suppressed levels of plasma  $\beta$ -hydroxybutyrate (ketones), suppressed levels of plasma free fatty acids and a glycaemic response to glucagon. Diagnosis should be made in consultation with an endocrinologist who is familiar with hyperinsulinism.

Neonates with suspected BWSp should be screened for hypoglycaemia (TABLE 6, R40 and R41) before discharge from the nursery. Neonates with confirmed hypoglycaemia should be treated to maintain a plasma glucose concentration  $>3.9$  mmol/l ( $>70$  mg/dL)<sup>134</sup>. Management of hyperinsulinism includes medical therapies such as diazoxide and somatostatin analogs (such as octreotide and lanreotide). Surgery (pancreatectomy) might be indicated if persistent hypoglycaemia occurs despite maximal medical therapies<sup>135</sup>. New therapies such as mechanistic target of rapamycin (mTOR) inhibitors (sirolimus) or glucagon-like peptide 1 receptor (GLP-1R) antagonists have been used in treatment of hyperinsulinism and very recently in BWSp<sup>136</sup>; however, to date, no specific management (medical or surgical) for hyperinsulinism has been evaluated in the context of BWSp (TABLE 6, R42).

Two genes that are implicated in congenital hyperinsulinism, *ABCC8* and *KCNJ11*, map to chromosome 11p, and, although rare, some patients with BWSp might carry a heterozygous mutation in either gene<sup>26</sup>. If these genes are included in the isodisomy, then homozygosity for the mutation in disomic cells produces severe hypoglycaemia<sup>26</sup>. In cases of hypoglycaemia with hyperinsulinism and without other traits suggestive of BWSp, investigations for 11p15.5 methylation abnormalities might be considered.

### Management of cardiac lesions

Congenital heart disease is more prevalent in BWS than in the general paediatric population and cardiac defects occur in up to 13–20% of patients with BWS<sup>11,16,22</sup> (TABLE 6, R44). Minor anatomical defects (for example, cardiomegaly, patent ductus arteriosus or patent foramen ovale and interatrial or interventricular defects) require echocardiographic monitoring until usual spontaneous resolution occurs (TABLE 6, R45). More severe defects might require surgical correction, although the management will be similar to that in sporadic cases of heart disease (TABLE 6, R47).

Congenital long QT syndrome has been reported in two families with BWS harbouring an intragenic deletion and a translocation at IC2 leading to inactivation of the *KCNQ1* gene, which, although very rare, is associated with a risk of sudden death (TABLE 6, R46)<sup>85,102</sup>.

### Management of neurological features

Cognitive development is usually normal in patients with BWSp; however, developmental delay can be associated with prematurity, severe hypoglycaemia, unbalanced chromosome rearrangements or paternal genome-wide UPD<sup>137</sup> (TABLE 6, R48). The differential diagnosis should be carefully considered in patients with presumptive BWS and learning disability and without a 11p15 anomaly, as some overgrowth disorders (for example, Sotos syndrome, Malan syndrome and Simpson–Golabi–Behmel syndrome) are more frequently associated with developmental delay<sup>30,138–144</sup> (Supplementary TABLE 2) (TABLE 6, R49).

Malformations of the central nervous system (for example, abnormal posterior fossae (including Dandy–Walker malformations) or abnormal corpus callosum or septum pellucidum) have been reported in rare patients with BWSp (chiefly with a defect involving IC2)<sup>83,145</sup>, and these features might need to be considered in children with neurological symptoms or signs (TABLE 6, R50).

### Management of renal complications

The prevalence of nephro-urological anomalies in BWSp is 28–61%<sup>146</sup>. A variety of anomalies have been described; cortical and medullary cysts occur in ~10% of patients with BWSp and the prevalence of hypercalciuria and nephrolithiasis is increased compared to the general population<sup>147</sup>. Although not all nephro-urological anomalies detected by ultrasonography will be of clinical significance, a minority of anomalies might be severe (and usually detectable prenatally), requiring medical or surgical management. Severe vesicoureteral reflux might cause kidney damage and recurrent urinary tract infections<sup>148</sup>. In addition, nephromegaly might be a marker of increased risk of Wilms tumour<sup>146</sup>.

Renal anomalies might occur in all molecular subtypes of BWSp, but only certain groups might be offered regular renal imaging for tumour surveillance. Management of the nephro-urological aspects of BWSp should be pragmatic and balance the benefits of presymptomatic diagnosis and treatment of critical obstructions and urinary tract infections for preserving renal function with the drawbacks of over-investigation for benign variants detected by surveillance. Thus, we recommend a nephrourological evaluation at clinical diagnosis and at the time of adult transition for any patient with BWSp, and screening for nephrocalcinosis and/or stones only in patients who undergo abdominal USS for tumour screening (TABLE 6, R51–55).

### BWSp and embryonal tumours

Embryonal tumours occur in ~8% of children with BWSp<sup>149</sup>. The most common types of embryonal tumour are Wilms tumour (52% of all tumours), hepatoblastoma (14% of all tumours), neuroblastoma (10% of all tumours), rhabdomyosarcoma (5% of all tumours) and adrenal carcinoma (3% of all tumours)<sup>13</sup>. Although there are some differences in mean age at diagnosis between tumour types, the overall cancer risk is highest in the first two years of life and clinical experience suggests that the cancer risk then declines progressively before puberty, approaching the cancer risk of the general population. Currently, there is no evidence of an increased risk of malignant tumours in adulthood (Supplemental TABLE 3).

The tumour risk correlates with the BWSp molecular subgroup; patients with segmental upd(11)pat and IC1 GOM have a higher tumour risk than patients with *CDKN1C* mutations and IC2 LOM<sup>58</sup>. The four main molecular subgroups are characterised by a cancer risk gradient, with the highest risk in cases of IC1 GOM (28% risk), followed by segmental upd(11)pat (16% risk), *CDKN1C* mutation (6.9% risk) and IC2 LOM (2.6% risk)<sup>13</sup>. In addition, there are also differences in the tumour types observed between molecular subgroups. Patients with IC1 GOM are mostly predisposed to developing Wilms tumour (observed in 24% of cases and accounting for 95% of malignancies in this group)<sup>13,14,149</sup>. Conversely, patients with IC2 LOM and *CDKN1C* mutations do not usually develop Wilms

tumour, but rather develop other tumours such as hepatoblastoma, rhabdomyosarcoma and neuroblastoma. Thus, a study from 2016 reported a prevalence of Wilms tumour of ~0.2% (2/995) in patients BWSp and IC2 LOM<sup>149</sup>; Although, a report from 2017 suggested that the risk of Wilms tumour in patients with IC2 LOM might be underestimated, only a single patient with Wilms tumour and an IC2 epimutation was observed<sup>150</sup> so that, when put together with previous reports of Wilms tumour in large cohorts of patients with BWSp, the overall prevalence of Wilms tumour with IC2 LOM is probably much less than 1%<sup>151</sup>. Patients with *CDKN1C* mutations are mostly predisposed to neuroblastoma<sup>13,14,149</sup>. Patients with segmental upd(11)pat are predisposed to develop any of the tumour types seen in BWSp (TABLE 3). Individuals with genome-wide paternal UPD seem to have a high risk of developing tumour types similar to those with segmental upd(11)pat, but with an increased incidence of hepatic and/or adrenal tumours extending into adolescence and young adulthood<sup>63,64,137,152</sup>.

Specific studies investigating the tumour risk in patients with isolated lateralized overgrowth and clinically diagnosed BWS with negative molecular testing are lacking. It seems plausible that the cancer risk in patients with isolated lateralized overgrowth who fall within the BWSp is linked to the type of 11p15.5 molecular anomaly. Indeed, the tumour risk in patients with isolated lateralized overgrowth and segmental upd(11)pat is estimated to be as high as 32–50%<sup>121,153</sup>.

### Tumour surveillance strategies

Tumour screening in patients with inherited cancer predisposition syndromes aims to improve patient survival and reduce morbidity through earlier detection of tumours. However, no surveillance protocol can detect every tumour and there are both benefits and drawbacks to screening — the latter include the financial costs, morbidity that can result from investigating asymptomatic benign lesions detected on surveillance, and psychosocial burden of repeated investigations for the patient and family. There is no generally accepted risk threshold for instigating tumour screening strategies and it might vary according to regional medical and medicolegal practices and local healthcare systems. Although screening is considered for a tumour risk >1% in the USA, a risk of 5% might be considered an appropriate threshold in Europe<sup>9,154</sup>. Various protocols have been suggested for tumour surveillance in BWSp, usually comprising abdominal USS with or without measurement of  $\alpha$ FP levels at various ages and intervals during infancy<sup>13,14,155</sup>. Traditionally, although most protocols have been applied to all cases of BWSp, the definition of specific epigenotype-tumour risk correlations provides a basis for more targeted surveillance protocols.

**Screening for Wilms tumour**—Abdominal USS is the preferred modality for Wilms tumour screening. The doubling time of Wilms tumour cells, has been estimated to be 11–13 days<sup>156</sup> and USS is recommended every 3–4 months<sup>157,158</sup>. Given the high survival rate of individuals with Wilms tumour (90% overall survival at 4 years), early detection of Wilms tumour by surveillance is predicted to only marginally impact survival; however, diagnosis at an earlier stage might reduce the burden of treatment-related morbidity<sup>159–162</sup>.

If Wilms tumour screening is targeted by BWSp molecular subgroup, patients with IC1 GOM and segmental upd(11)pat are at the highest risk and several groups have suggested that patients with IC2 LOM should not be screened using USS in order to avoid excessive medicalization and possible false-positive results<sup>149,154</sup>.

**Screening for hepatoblastoma**—The risk of hepatoblastoma in patients with BWS is >2000-fold higher than in the general population and hepatoblastoma is the second most common tumour type in BWS<sup>20</sup>. However, specific studies evaluating hepatoblastoma screening in BWSp are lacking. Abdominal USS is a first-line investigation in children with a suspected liver mass, although not all parts of the liver can be imaged easily and small tumours might be missed<sup>159</sup>. Concerns about the sensitivity of abdominal USS led to suggestions that it should be combined with measurements of serum levels of  $\alpha$ FP, which is secreted by >95% of hepatoblastomas<sup>163–165</sup>. Treatment and outcome of patients with hepatoblastoma is closely connected to tumour stage at diagnosis, and preliminary data suggested that patients with BWSp and hepatoblastoma who are screened for  $\alpha$ FP have an earlier stage at diagnosis and a better prognosis than unscreened patients, and that increased serum  $\alpha$ FP levels might precede hepatoblastoma detection by USS<sup>166</sup>. However, this hypothesis is unproven and further data is required. In the paediatric setting, interpreting serum  $\alpha$ FP levels can be complex due to the wide range and variable concentrations in early infancy<sup>167,168</sup>. Serum  $\alpha$ FP levels might be higher in babies with BWS and without hepatoblastoma than in normal age-matched healthy controls<sup>169</sup>. In view of the burden of repeated venepuncture and the complexity of interpreting elevated  $\alpha$ FP levels, it has been debated whether the benefits of  $\alpha$ FP screening in BWSp outweigh the drawbacks<sup>170–173</sup> and the consensus voted not to recommend  $\alpha$ FP screening (TABLE 6, R64).

**Screening for neuroblastoma**—Although reported in all BWSp molecular subgroups, neuroblastomas are preferentially associated with *CDKN1C* mutations with a frequency of ~4%<sup>13</sup> (TABLE 3). Detection of asymptomatic neuroblastomas by determination of the urinary tumour markers vanillylmandelic acid and homovanillic acid and/or the catecholamine to creatinine ratio, combined with three monthly USSs until age 2–3 years has been suggested<sup>149</sup>. However, previous neuroblastoma screening strategies using urinary markers in large-scale paediatric settings had a very minor influence on the related morbidity and mortality rates<sup>174,175</sup> and there is currently no evidence that neuroblastoma screening in BWSp improves treatment and survival (TABLE 6, R65).

**Surveillance for other tumour types**—Screening for adrenal carcinoma can be undertaken using clinical evaluation, adrenal USS and determination of serum dihydroepiandrosterone sulfate (DHEAS) concentrations every 4–6 months<sup>176</sup>. However, adrenal carcinoma is rare in BWS (even in patients with genome-wide paternal UPD who are at highest risk) and there is no data on the utility of such screening strategies in BWSp.

### Consensus tumour surveillance protocol

The Consensus group agreed that tumour surveillance should be targeted to those molecular subgroups of BWSp that are at highest risk and that children with BWSp and IC2 LOM should not be offered routine USS (TABLE 6, R60) (although there should be a low

threshold for investigation in response to symptoms or parental concern). Other BWSp molecular subgroups and patients with classical BWS and no detectable molecular anomaly should be offered abdominal USS every 3 months until age 7 years (TABLE 6, R57–59 and R61–63) (TABLE 3). It was agreed that  $\alpha$ FP measurements should not be offered routinely because the incidence of HB was judged too low to warrant specific screening, the influence of surveillance of patients and families is unclear and the difficulties in interpretation might lead to false positive results (TABLE 6, R64). Nevertheless, in specific healthcare systems, clinicians might currently vary from the proposed protocol, especially when regional protocols are available, pending the outcome of the results of prospective studies of targeted and universal surveillance.

The consensus surveillance protocol enables ~50% of children with BWSp at low tumour risk to be spared 3 monthly USSs and, although the risk of Wilms tumour for example is small in patients with a *CDKN1C* mutation, applying a common surveillance modality (abdominal USS rather than renal USS in some subgroups, liver USS in other subgroups *et cetera*.) in all the groups to be screened avoids the potential for confusion with more complicated regimens. It should be noted that the agreed protocol differs from that recommended recently by the American Association for Cancer Research (AACR) Childhood Cancer Predisposition Workshop, who adopted a 1% risk threshold for surveillance and therefore recommended abdominal USS and  $\alpha$ FP screening for all cases of BWSp<sup>155</sup>. Both the AACR group and this Consensus group made these decisions based on similar data for tumour risks in different molecular subgroups, but came to differing conclusions with regard to adopting a targeted screening approach. It should be noted that the AACR group consisted predominantly of experts from North America, whereas the International BWS Consensus group was composed predominantly of experts from European centres where targeted screening has already been adopted in some countries<sup>13,154</sup>. Thus, the difference in screening recommendations between the two groups reflects mainly the different medical and medicolegal cultures in North America and Europe. Although a universally agreed screening protocol would usually be preferable, taking into account the different conclusions between the AACR group and this consensus groups experts, it is reasonable that at this time, screening protocols could be different between Europe and North America. Such diversity of practice can be helpful as careful audit of the results of the two protocols can help further refine our recommendations at future international consensus meetings<sup>155</sup>.

### Management of BWSp-related tumours

Children with BWSp and Wilms tumour, when compared with non-syndromic children with Wilms tumour, present with less metastatic disease because of earlier-stage disease, fewer anaplastic tumours and a higher incidence of bilateral synchronous or metachronous recurrence<sup>1610</sup> (TABLE 6, R67). The latter seem to be connected to the presence of multifocal or diffuse nephrogenic rests in one or both kidneys (nephroblastomatosis)<sup>177</sup>, a feature that is not easily distinguishable from Wilms tumour on standard imaging<sup>160</sup>. Although patients with BWSp and Wilms tumour who are diagnosed using abdominal USS surveillance have a smaller tumour size than children with sporadic Wilms tumour<sup>157</sup>, overall survival rates are similar (at least 90% at 4 years)<sup>161</sup>. Smaller Wilms tumours are

more amenable to partial nephrectomy and nephron sparing strategies (such as partial nephrectomy) are particularly preferred in patients with BWSp given the potential co-occurrence of progressive non-malignant renal diseases and bilateral Wilms tumours<sup>158</sup>. Data from 2016 show comparable outcomes after nephron sparing surgery and total nephrectomy in patients with BWSp and Wilms tumour<sup>160</sup>.

### Late-onset complications

Features of BWSp such as macroglossia and postnatal overgrowth tend to ameliorate with age and therefore BWSp is often likely overlooked in adults unless there is a prior diagnosis in childhood. There is a paucity of information on long-term outcomes and late-onset complications in adults with BWSp (R70). Concerns about potential adult-onset complications that are not directly related to childhood features of BWSp fall into four areas.

**Neoplasia**—Despite the link with embryonal neoplasia, there is no apparent association between BWSp and predisposition to common adult-onset carcinomas. Although rare endocrine tumours have been reported in adults with BWSp<sup>62,152,178–180</sup> (Supplementary TABLE 3), there is no evidence of a specific tumour risk that might justify surveillance. However, follow-up of large series of adults with BWS have not been performed. Children with BWSp who are treated for embryonal tumours might develop late-onset complications from surgery, radiotherapy or chemotherapy, similar to children with sporadic tumours.

**Cardiovascular defects**—Patients with congenital heart disease require appropriate follow-up in adult specialty clinics. Although rare, cardiovascular defects might be diagnosed for the first time in adulthood<sup>181</sup>, but routine screening is not indicated. Patients with rare IC2 CNVs and/or rearrangements that might predispose to long QT syndrome require follow-up throughout adulthood.

**Infertility**—Although congenital anomalies of the urogenital tract (for example, bicornuate uterus) have been described in BWSp<sup>178,181</sup>, there is no clear evidence of excess fertility problems in women with BWSp. Reduced fecundity has been described in affected males (compared to females)<sup>182</sup>, but the frequency of infertility in men with BWSp is unknown.

**Renal anomalies**—Although examples of the diagnosis of renal anomalies in adults with BWSp have been reported<sup>178</sup>, it is assumed that, if renal USS was performed, renal abnormalities would usually be detected in childhood.

Although regular surveillance (for example, echocardiography, renal function testing and evaluation of hearing) has been suggested for adults with BWSp<sup>181</sup>, in the absence of abnormalities detected during childhood surveillance, the detection rate of such investigations in asymptomatic adults with BWSp is likely to be low and could pose problems with health insurance. The consensus group agreed that a detailed clinical review and renal USS (Supplementary TABLE 4) should be undertaken at age 16 years and specific recommendations for continued surveillance based only on ongoing problems were agreed (TABLE 6, R68). Adults with BWSp should be encouraged to seek genetic counselling advice before starting a family (TABLE 6, R69). At that stage, any potential concerns about fertility can be reviewed and referrals for further investigation made as appropriate.

## Psychological and counselling aspects

The diagnosis of a disorder such as BWSp can have wide-ranging effects on the psychological and social wellbeing of families. Although the precise effects will vary between families and will be influenced by individual medical and social factors, and considering that each family might face different challenges, it is important that all healthcare professionals are aware of the wider non-medical issues that might be relevant to the family (TABLE 6, R71). Information on the psychosocial aspects that might be specific to BWSp is sparse. In many cases there is no previous relevant family history and the parents are not prepared for the diagnosis. Issues such as tumour risk can be worrying and it is apparent that differing medical practices and recommendations might cause parental uncertainty and anxiety. A survey of parents of children with BWSp who have macroglossia revealed widespread parental concerns about the “negative cosmetic appearances” of a large protruding tongue and persistent drooling, which led to strangers staring and questioning whether their children had learning difficulties<sup>128</sup>. Parents are also concerned that this might lead to teasing by other children and a retrospective questionnaire survey revealed an apparent increase in emotional difficulties and problems with peers in children with BWSp<sup>183</sup>. Healthcare professionals should be aware that psychosocial difficulties might occur and should be prepared to refer families to specialists such as genetic counsellors, social workers and psychologists, as appropriate. As support groups can have key roles in helping families adjust to the diagnosis, share their concerns and experiences and obtain the correct care and support, all families should be given the contact details of relevant groups (TABLE 6, R72).

## Conclusions

The recommendations of the first international BWS consensus group described in this Consensus Statement provide a framework for improving the diagnosis and management of BWSp. As BWSp is characterised by complex genetics and variable multisystem phenotypes, it is important that a lead clinician is identified for each patient (TABLE 6, R22) to ensure coordination of the numerous aspects of care throughout childhood (Supplementary TABLE 4). The proposed diagnostic and care pathways are intended to be practical and cost effective (for example, targeting tumour surveillance to high-risk groups should reduce costs compared to universal surveillance strategies). Nevertheless, in some healthcare systems and medicolegal environments, further evidence might be required to shift clinical practice (for example, tumour surveillance in North America). Thus, it is important that implementation of these consensus recommendations should be accompanied by prospective audits in order to expand the evidence base for future consensus initiatives.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Biographies

Frédéric Brioude is Associate Professor and Pediatric Endocrinologist at Armand Trousseau Hospital, Paris, France. He focuses on the clinical care and molecular diagnosis of Beckwith–Wiedemann syndrome (BWS) and Silver–Russell syndrome. He has 29 PubMed publications, most of them about imprinting disorders and Beckwith Wiedemann syndromes. He gave several lectures about BWS/SRS in France and in international meetings (European Society for Pediatric Endocrinology, European Society of Human Genetics).

Jennifer M. Kalish is an Assistant Professor of Paediatrics and Genetics at the Perelman School of Medicine at the University of Pennsylvania and Children’s Hospital of Philadelphia, United States. Her research interests include the molecular basis of epigenetic and cancer predisposition disorders, specifically how epigenetic changes lead to tumour formation. She co-authored the Clinical Cancer Research Paediatric Oncology Series guidelines and has published on the clinical spectrum of BWS.

Alessandro Mussa is Staff physician at the NICU of the Città della Salute e della Scienza in Torino, Italy, and Consultant at the Department of Paediatrics, Faculty of Medicine, Torino for the Clinics of Imprinting Disorders as an expert in their management. He is a member of the Scientific Committee of the Italian BWS Association and author of the Italian Recommendations for Beckwith–Wiedemann syndrome. He is also an author of over 70 publications in the field of paediatric endocrinology, metabolism and genetics, and has authored several papers on Beckwith–Wiedemann syndrome.

Alison Foster is a doctoral research fellow in the Institute of Cancer and Genomic Sciences at the University of Birmingham, UK, and a registrar in Clinical Genetics at Birmingham Women’s and Children’s NHS Foundation Trust hospitals. Her interests include rare genetic overgrowth disorders. She is Chief Investigator for the Phenotyping of Overgrowth Disorders (POD) study funded by the NIHR Rare Diseases Translational Research Collaboration.

Jet Blik is Laboratory Lead, Academic Medical Center Department of Clinical Genetics, University of Amsterdam, Netherlands. Her interests include basic and clinically applied research on the genetic aetiology of Beckwith–Wiedemann syndrome and associated childhood tumours; genomic imprinting; innovation of DNA-diagnostics for imprinting disorders; mechanisms of genomic imprinting; and epigenetic gene regulation in clinical conditions including trauma, child abuse and neglect and foetal alcohol syndrome. She has 44 publications including development and validation of novel diagnostic methods and epigenotype–phenotype correlations in imprinting disorders

Giovanni Battista Ferrero is Associate Professor of Paediatrics in the School of Medicine, University of Torino and Honorary Consultant in Clinical Genetics at Regina Margherita Children’s Hospital, Torino. His career interests are in genetics, epigenetics and clinical characterization of childhood developmental disorders, as evidenced by over 100 PubMed research publications, including description of (epi)genotype–phenotype correlations in

Beckwith–Wiedemann syndrome and imprinting defect risk in children conceived through assisted reproductive technologies

Susanne E. Boonen is a Consultant in Clinical Genetics at Zealand University Hospital, Roskilde, Denmark. Her career interests are in clinical genetics and epigenetics especially imprinting disorders. The title of her PhD thesis was “Clinical Consequences of Hypomethylation of Imprinted Loci due to Defective ZFP57” mainly focusing on transient neonatal diabetes mellitus and Beckwith–Wiedemann syndrome and describing the genotype-epigenotype-phenotype of these patients. She has 16 PubMed publications mainly on multi-locus imprinting disturbances.

Trevor Cole is Consultant in Clinical and Cancer Genetics, and Rare Disease Lead for the West Midlands Genomics Medicine Centre. He has a long-standing clinical and strategic interest in the development and delivery of services for rare genetic diseases. Formerly Chair of the Joint Royal Colleges Committee for Medical Genetics and Deputy Chair of the NICE Highly Specialised Technologies Committee. He is Current Chair of the UK GTN Rare Disease Service Improvement Group and Department of Health Working Group on the Diagnostic Odyssey. Published >160 peer reviewed papers, 47 on overgrowth disorders and paediatric cancer genetics and 4 book chapters.

Robert Baker is the founder and co-ordinator of the Beckwith–Wiedemann Support Group UK which has been running since 1987. It currently has over 200 family members and is working with Great Ormond Street Hospital to support their BWS macroglossia service. The support group aims to disseminate information about BWS to families of affected children. Its website can be found at [bwssupport.org](http://bwssupport.org)

Monica Bertoletti is the mother of a child with BWS. Involved with the Italian Beckwith–Wiedemann patient support group (Aibws Onlus) since 2005, as President from 2009 to 2012 and as CEO from 2012 to present. She is a volunteer certified as an expert in youth communication, expertise in public relations and event organisation.

Guido Cocchi is Associate Professor at the Alma Mater Studiorum, University of Bologna. He is Head of Outpatient of Rare Diseases of the Neonatology Unit of S. Orsola Hospital, Bologna, Italy. He is also Director of the IMER (Births Defects Registry of the Emilia-Romagna Region) in the International Clearinghouse for Birth Defects Monitoring System. He has published more than 100 papers on births defects surveillance and genetic and chromosomal abnormalities.

Carole Coze is Associate Professor and Pediatric Oncologist at la Timone Childrens Hospital and Aix-Marseille University, Marseille, France. She is a Member of the French Society of Paediatric Oncology (SFCE). She focuses on the clinical care for paediatric solid tumours and lymphomas and is investigator in research programs on paediatric abdominal cancers (mainly neuroblastoma) and on late effects. She has over 100 PubMed publications across these topics.

Maurizio De Pellegrin is Head of the Functional Unit of Paediatric Orthopaedics and Traumatology at the San Raffaele Hospital in Milan. He is an Associate Professor and teaches Paediatric Orthopaedics and Traumatology at the Faculty of Medicine of the Vita-Salute University-San Raffaele in Milan. He is an Orthopaedic Consultant for the Italian Societies of Mucopolysaccharidosis and Prader–Willi, Down, Beckwith–Wiedemann and Moebius syndromes. Fields of major interest in Paediatric Orthopaedics: developmental dysplasia of the hip, paediatric foot deformities, congenital limb and spine deformities, rare diseases, limb lengthening, basic research of rare diseases

Khalid Hussain is a Professor of Paediatric Endocrinology and Program Director for Research at Sidra Medical and Research Centre, Doha Qatar. His research interests focus on understanding the biochemical and molecular mechanisms of childhood hypoglycaemia, especially hyperinsulinaemic hypoglycaemia. He has published over 300 manuscripts in the field of childhood hypoglycaemia.

Abdulla Ibrahim is a senior house officer at North Bristol NHS Trust, UK. His MSc(Res) was based on methylation analysis and diagnostics of Beckwith–Wiedemann syndrome which included the identification of epigenotype–phenotype associations and the development of a clinical scoring system for the prediction of positive methylation abnormalities

Mark Kilby is Professor of Fetal Medicine in the Centre of Women’s and New-born Health and the Institute of Metabolism & Systems Research at the University of Birmingham, UK. He is also Clinical Lead for the Fetal Medicine Centre at Birmingham Women’s & Children’s Foundation Trust, Birmingham, UK. He holds grants from the Wellcome Trust, MRC (EME), NIHR HTA and Wellbeing of Women. He has 270 PubMed cited publications and is the author/Editor of numerous books and review articles.

Malgorzata Krajewska-Walasek is Head of the Medical Genetics Department at the Children’s Memorial Health Institute in Warsaw, Poland. She is a specialist in paediatrics, clinical genetics and laboratory medical genetics. Her particular interest lies in the identification and characterisation of rare genetic dysmorphic syndromes. Also, she focuses on basic and clinically applied research on the genetic aetiology of imprinting disorders, including BWS. She acted as the Polish Coordinator of UE Projects: DYSCERNEA European Network of Centres of Reference for Dysmorphology (2007–2010); ORPHANET EUROPE (2011– 2014); ORPHANET – RD-ACTION (2015–2018) and COST Action European Network for Human Congenital Imprinting Disorders (2012–2017).

Christian Kratz professor in Paediatrics and Director of the Department of Paediatric Haematology and Oncology; He co-chairs the German Fanconi Anemia Registry and the Cancer Predisposition Working Group of the German Society of Paediatric Haematology and Oncology. Together with Stefan Pfister he has launched a registry for patients with Li-Fraumeni syndrome and other cancer predisposition syndromes, including Beckwith–Wiedemann syndrome. His main aim and motivation is to improve the lives of individuals with an increased cancer risk, as evidenced by over 100 PubMed publications in this area

including key publications on the discovery of germline *KRAS* mutations in Noonan syndrome.

Edmund Ladusans trained in Paediatric Cardiology at Guy's & Harefield Hospitals London, UK. Previously Consultant Cardiologist & Lead for Paediatric Catheter Interventional Treatments Alder Hey Hospital Liverpool UK (2000–2015). Currently Clinical Lead for Paediatric Cardiology, Royal Manchester Children's Hospital, UK (2015–Current). Special interests in paediatric cardiac arrhythmias and inherited cardiac disease. Paediatric Cardiology advisor to William's Syndrome Foundation UK (2009–2015), contributor to WSF National medical guidelines published 2009.

Pablo Lapunzina is Director of, Institute of Medical and Molecular Genetics, University Hospital La Paz, Autónoma University of Madrid, Spain. His focus is on dysmorphology, clinical genetics and specifically, overgrowth syndromes, genomic rearrangements and discovery of new genes. He is also the Scientific Director of CIBERER (National Network Center of Research for Rare Diseases. ISCIII, Madrid). Pediatrician, Clinical and Molecular Geneticist, and Specialist in Embryofetal Medicine. He is author of over 170 articles in the medical and scientific literature, 9 book chapters, and 5 books.

Yves Le Bouc is a paediatric endocrinologist, Professor of Physiology at the Pierre and Marie Curie-Paris VI University (UPMC), and formerly Head of the Paediatric Endocrine Investigation Department and the Molecular Diagnosis Laboratory concerning growth disorders at Armand-Trousseau Children's Hospital in Paris. Currently Director of an Inserm research team studying IGF System. He is particularly involved, for ~30 years, in understanding the molecular abnormalities concerning BWS and published for the first epigenetic abnormality of the Silver–Russell Syndrome at the 11p15 chromosomal region. Published nearly 200 original clinical and scientific studies focusing on foetal and postnatal growth disorders.

Saskia Maas is a clinical geneticist at the department of clinical genetics in the Academic Medical Center in Amsterdam. Her career is focused on diagnosis, clinical care and research on Beckwith-Wiedemann syndrome and other overgrowth disorders.

Fiona Macdonald is a graduate of Edinburgh University and carried out her PhD research at the University of Leicester, UK. She has worked in the diagnostic molecular genetics laboratory in Birmingham since 1988 as head of the Molecular Genetics section of the West Midlands Regional Genetics Service subsequently as deputy director of the laboratory from 2011–2014. Currently she is scientific adviser to the UK Genetic testing network. She has over 60 publications in the field of molecular genetics.

Katrin Õunap is a Paediatrician and Clinical Geneticist, Full Professor and the Head of the Department of Clinical Genetics, United Laboratories, Tartu University Hospital and Institute of Clinical Medicine, University of Tartu, Estonia. Her special interest is in clinical and molecular aspects of inherited rare disorders including Beckwith–Wiedemann syndrome. She has over 95 original publications in PubMed. Among them 10 publications on the topic of imprinting disorders.

Licia Peruzzi is Chief of the Paediatric Kidney Transplant Center in the Paediatric Nephrology Unit. She is Professor of Paediatric Nephrology, Paediatric Nursing School and Specialization School of Paediatrics University of Turin, Italy. Co-author of 98 papers from Pub Med, Hirsch Index: 28. Member of the European Society for Paediatric Nephrology where is part of Inherited Renal Diseases Working Group, board member of the Immune Mediated renal disorders and Kidney Transplantation Working Groups. Consultant and clinical carer for paediatric inherited, syndromic and rare kidney diseases from prenatal diagnosis to transition to adult centres.

Sylvie Rossignol is Professor of Pediatrics at Strasbourg University School of Medicine, France. She completed a fellowship in Pediatric Endocrinology at the department of “Explorations Fonctionnelles Endocriniennes” at the Trousseau Children Hospital, Paris, supervised by Prof Yves Le Bouc. She undertook research on the epigenetic regulation of the 11p15 region in BWS and Silver–Russell syndromes obtaining her PhD from Pierre et Marie Curie University, Paris. Research interests include prospective studies of growth and phenotype in BWS and SRS, molecular mechanisms of imprinting at 11p15 including the role of environment (especially ART) in the occurrence of the epimutations.

Silvia Russo is Group leader for diagnostic and research activities of rare Mendelian diseases and Imprinting Disturbances (BWS, Silver–Russell, Angelman/Prader–Willi, Cornelia de Lange, X-linked Mental Retardation) and multifactorial disease including Autism) at Molecular Branch of the Cytogenetics and Molecular Genetics Laboratory, Istituto Auxologico Italiano, Milan. Member of the Italian National BWS Association. Interested in epigenetic disorders and specially focused on mosaicism of imprinting disorders. She is also involved in BWS research, aiming to identify novel disease mechanisms by applying genomic tools (exome sequences, SNParray) and to investigate the origin of the epigenetic defects (Mutations in trans acting genes).

Caroleen Shipster MRSLT MSc is a Specialist Speech and Language Therapist and Lead Clinician for the Macroglossia Service for children with Beckwith-Wiedemann syndrome at Great Ormond Street Hospital for Children, London. This is a specialised service designated by NHS England and provides treatment for all the children in the UK who have macroglossia associated with BWS. She is the SLT Team Leader for the Craniofacial Unit at GOSH. Her research interests include macroglossia in BWS and communication difficulties in craniofacial difficulties.

Agata Skórka is a Paediatrician and Senior Lecturer of paediatrics and clinical genetics at the Department of Pediatrics of Medical University of Warsaw with special interest in paediatric endocrinology and nutrition. She is also Consultant in Clinical Genetics at the Department of Medical Genetics of The Children’s Memorial Health Institute, Warsaw, Poland. Her special interest is in clinical and molecular aspects of dysmorphic syndromes, recently she became involved in the project of clinical characterisation of the large group of Polish patients with Beckwith-Wiedemann syndrome. She has several PubMed publication in the field of paediatrics and genetics

Katrina Tatton-Brown, a Consultant Clinical Geneticist and Reader in Clinical Genetics and Genomic Education, works at St George's University Hospitals NHS Foundation Trust, St George's University of London and the Institute of Cancer Research. Her research thesis investigated the molecular and phenotypic spectra of Sotos syndrome. She has a strong research and clinical interest in overgrowth conditions, including BWS, and has published widely in this area. She is very involved with education and training and has developed several genomics MOOCs that have been globally accessed, a postgraduate certificate in clinical genomics and leads the Clinical Genetics training scheme in London.

Jair Tenorio is a molecular geneticist (MSc, PhD) at the Institute of Medical and molecular geneticist and part of the CB06/07/1005 CIBERER (Centro de Investigación Biomédica en Red de Enfermedades Raras) group, Madrid, Spain. His thesis was focus on the molecular basis of overgrowth syndromes, including Beckwith-Wiedemann Syndrome. During his thesis he was able to detect mutations in one gene (RNF125) related to a new overgrowth entity which nowadays is known as Tenorio syndrome (MIM#616260). He has 20 publications related not only with overgrowth and imprinting disorders, but also other genetic disorders.

Chiara Tortora Graduated in Dentistry in 2004 and specialised in Orthodontics in 2008 at University of Milan. Orthodontic Consultant at the SMILE HOUSE, regional centre for cleft lip and palate, Saints Paolo and Charles, Milan (Clinical Coordinator, Dott. Luca Autelitano). Member of the scientific committee for AIBWS (Beckwith-Wiedemann Syndrome) and member of the SILPS (Italian society for the study and the treatment of cleft lip and palate patients). Author of many national and international scientific articles.

Karen Grønskov is a Senior Scientist, Clinical Genetic Clinic, Kennedy Center, Rigshospitalet, University of Copenhagen, Denmark. Her research interests include identification of (epi)genetic mechanisms involved in eye development and diseases such as oculocutaneous albinism, retinal dystrophies, microphthalmia, optic atrophy, glaucoma and aniridia, as well as genetic causes of imprinting disorders including Beckwith-Wiedemann and Silver-Russell syndromes. She was a Working group co-leader in COST Action BM1208 – EUCID.net on imprinting disorders. She has 71 publications, including papers on genetic rearrangements and mutations underlying imprinting disorders.

Irène Netchine is Professor of Physiology at Pierre & Marie Curie School of Medicine, Armand Trousseau Children's Hospital, Paris; coordinator of the Departments of Paediatric Endocrinology and the Molecular Diagnosis Laboratory concerning growth disorders, and INSERM research team leader. A research pioneer in Silver-Russell syndrome (SRS) with 60 publications, her current research includes the role of the IGF system in IUGR and imprinting anomalies leading to fetal growth disorders. She instigated the French multidisciplinary clinical services for SRS and BWS; Vice-chair COST Action BM1208–EUCID.net on imprinting disorders; ESPE research unit coordinator; Chair of the first SRS International Consensus

Raoul CM Hennekam is Professor of Pediatrics and Translational Genetics at the Academic Medical Center in Amsterdam, Netherlands. He focusses on intellectual disabilities, autism,

aging, tumor predisposition syndromes, connective tissue disorders, natural history studies and (molecular) dysmorphology. He is author of >500 papers in peer-reviewed journals, including a series of papers on Beckwith-Wiedemann syndrome and other disorders in which imprinting plays a role.

Dirk Prawitt is a Full Professor of Molecular Paediatrics, Faculty of Medicine at the Center for Paediatrics and Adolescent Medicine, University Medical Center of Mainz, Germany. His research interests are in mechanisms of genomic imprinting, epigenetic gene regulation and translational research on clinical conditions, especially the Beckwith–Wiedemann syndrome and associated childhood tumours. He is a member of the German Society of Human Genetics and he is a Management Committee Member for COST Action BM1208 – EUCID.net on imprinting disorders. He has 48 PubMed publications including key publications on ICR1 function and a paediatrics textbook contribution (Lentze-Schaub-Schulte-Spranger).

Zeynep Tümer is Professor and Chief of R&D, Applied Human Molecular Genetics, Kennedy Center, University of Copenhagen, Denmark. She has 20 years experience in classic and molecular cytogenetics and has been leader of cytogenetics (Medical Genetics Clinic, ICMM, KU) for 4 years. Principal research interest is use of genomic technology to define genetic and/or epigenetic mechanisms of brain and/or neurological disorders such as Menke disease, Tourette syndrome, intellectual disabilities, developmental and congenital disorders. She is a ESHG Board member and Working Group Leader in COST Action BM1208–EUCID.net on imprinting disorders. She has >160 peer-reviewed publications spanning a broad range of human genetic disorders.

Thomas Eggermann is Associate Professor for Human Molecular Genetics at RWTH University, Aachen, Germany. He leads the molecular diagnostic unit at the Institute of Human Genetics, Aachen. His research interests are focused on the molecular genetics and pathomechanisms of 11p-associated imprinting disorders, as well as of chromosomal and monogenetic congenital disorders in general. He has published more than 250 manuscripts in the field of human genetics.

Deborah J. G. Mackay is Professor of Medical Epigenetics, Faculty of Medicine, University of Southampton, UK. Her research interests are in identification of genetic and epigenetic causes of imprinting disorders, including definition of the archetypal multi-locus imprinting disorder, and identification of causative mutations in ZFP57 and NLRP5. She is a Working Group Leader in COST Action BM1208 – EUCID.net on imprinting disorders. She has over 80 publications in research and diagnosis of human imprinting disorders.

Andrea Riccio is Professor of Genetics at DiSTABiF, University of Campania “Luigi Vanvitelli”, Italy. His research interests include molecular bases of genomic imprinting and associated human disorders, definition of cis-acting elements and trans-acting factors of imprinting control regions and identification of genetic and epigenetic causes of BWS. He has been co-author of EMQN guidelines for molecular diagnosis of BWS and SRS, coordinator of EC ITN INGENIUM on imprinting mechanisms and human disorders and

working group leader in COST Action BM1208 – EUCID.net on imprinting disorders. He has over 60 publications in research on genomic imprinting.

Eamonn R Maher is Professor of Medical Genetics and Genomic Medicine, Head of the Department of Medical Genetics at University of Cambridge; honorary consultant in clinical genetics at Cambridge University Hospitals; Chair of the first BWS International Consensus. Previously Professor of Medical Genetics and Director Centre for Rare Diseases and Personalised Medicine at University of Birmingham. Current research funding includes a ERC Advanced Researcher Award and NIHR Senior Investigator Award. His research interests include clinical and molecular aspects of inherited cancer predisposition syndromes and genomic imprinting disorders. He had a H-index of 90 and had published >400 research articles and reviews.

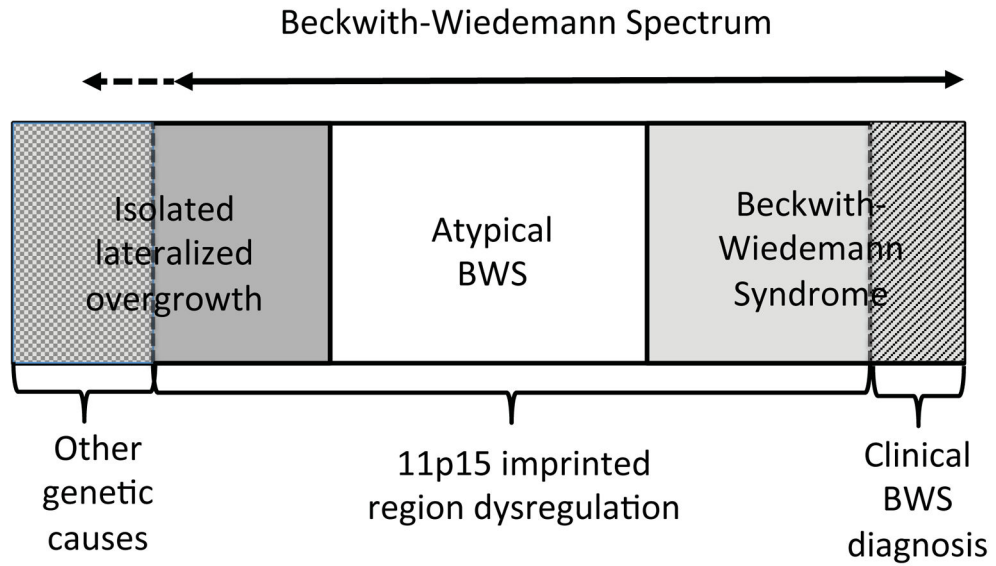
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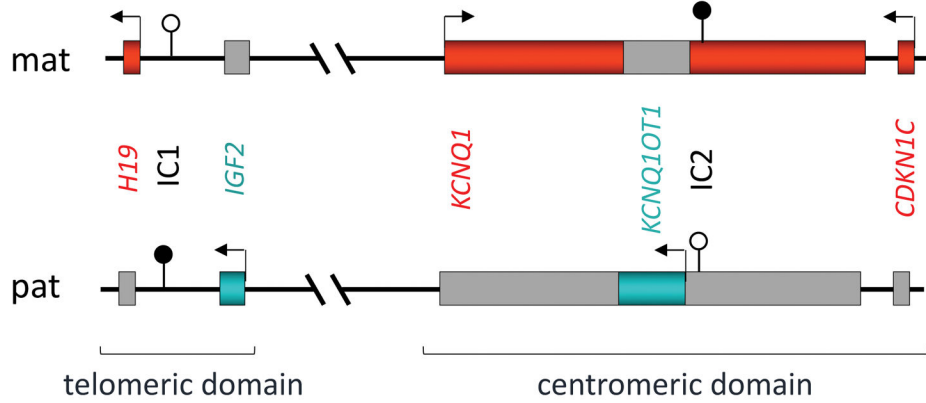
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**Figure 1. The Beckwith–Wiedemann spectrum**

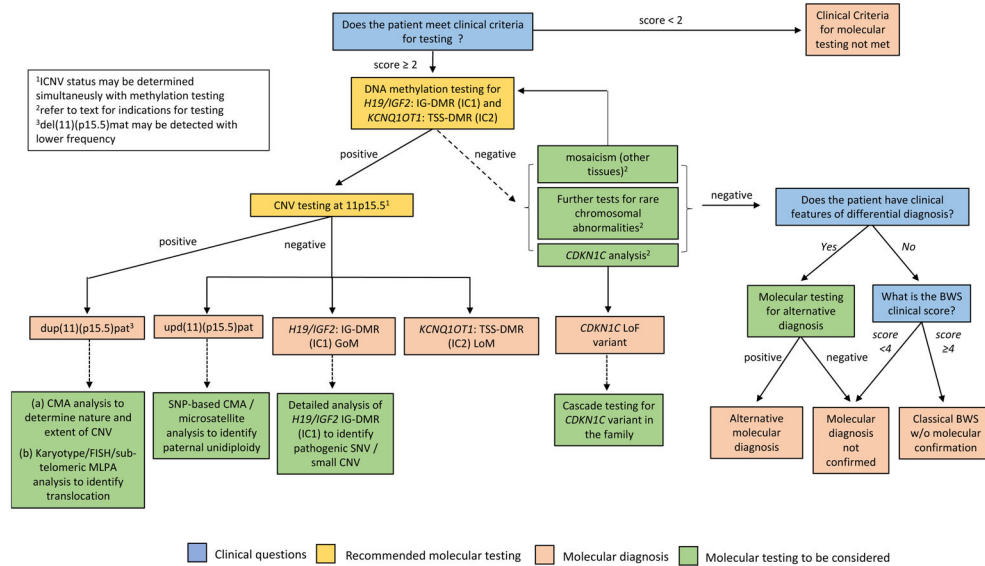
The Consensus group introduced the concept of Beckwith–Wiedemann Spectrum (BWSp) that includes patients with a clinical diagnosis of Beckwith–Wiedemann syndrome (BWS) with or without an (epi)genetic change at the BWS locus on chromosome 11p15; patients with ‘atypical BWS’ (defined as fewer cardinal and suggestive features than those needed for a clinical diagnosis of BWS) and an (epi)genetic change at the BWS locus; and patients with ‘isolated lateralised overgrowth’ and an (epi)genetic change at the BWS locus. The dotted arrowed line indicates that some patients with apparent isolated lateralised overgrowth and no 11p15 abnormality might subsequently be found to have an 11p15 abnormality on testing of additional tissues or with a more sensitive assay. Patients with clinical BWS and no detectable 11p15 abnormality might be further investigated with additional clinical evaluation and consideration of other syndromes which may have features overlapping with BWSp and appropriate testing for those syndromes may be warranted.



**Figure 2. The Beckwith–Wiedemann syndromelocus at chromosome 11p15.5**

The figure depicts the chromosome 11p15.

–11p15.4 region with the imprinted genes and control regions that are implicated in the pathophysiology of BWSp. The BWSp locus can be divided in two functionally independent domains, the telomeric and centromeric domains. Each domain harbours its own imprinting control region that is differentially methylated on the maternal and paternal chromosomes. The insulin-like growth factor 2 encoding gene *IGF2* and the gene encoding the non-translated long non-coding RNA (lncRNA) *H19* are located in the telomeric domain and are controlled by the *H19/IGF2:IG* DMR (Imprinting Centre 1, IC1) that is methylated on the paternal chromosome. The cell cycle inhibitor gene *CDKN1C* and the gene encoding the regulatory long non-coding RNA *KCNQ1OT1* are located in the centromeric domain and are controlled by the *KCNQ1OT1:TSS* DMR (Imprinting Centre 2, IC2) that is methylated on the maternal chromosome. Genes expressed from the maternal chromosome are depicted as red boxes and genes expressed from the paternal chromosome as blue boxes. Grey boxes indicate non-expressed alleles. Filled lollipops indicate methylated ICs and open lollipops indicate unmethylated ICs. Bent arrows indicate the orientation of transcription.



### Figure 3. Flowchart for investigation and diagnosis of Beckwith–Wiedemann syndrome

The figure summarises the molecular diagnostic pathway for investigation of suspected BWSp. Patients with clinical features reaching a score of  $\geq 2$  should be genetically tested. *H19/IGF2:IG-DMR (IC1)* and *KCNQ1OT1:TSS-DMR (IC2)* methylation are recommended as first-line molecular testing. If not estimated simultaneously with DNA methylation, DMR copy number should then be determined in all cases with IC1 and/or IC2 methylation abnormalities. If positive, these assays lead to the molecular diagnosis of BWSp with IC2 LOM, IC1 GOM, segmental upd(11)pat or CNV (most commonly dup(11)(p15.5)pat). Further molecular tests can be considered to determine underlying mechanism of methylation abnormality, UPD or CNV. If DNA methylation testing is negative, further molecular tests can be considered to identify mosaic methylation abnormalities, pathogenic *CDKN1C* variants or rare balanced chromosomal rearrangements. If all molecular tests are negative, differential diagnosis should be considered. However, a diagnosis of classical BWS is made in presence of a clinical score of  $\geq 4$  even in absence of the molecular confirmation of an 11p15 anomaly. Clinical questions are in blue boxes, recommended molecular tests in yellow boxes, molecular diagnoses in pink boxes, molecular testing to be considered in green boxes. CMA, chromosome microarray analysis, which can be oligonucleotide- and/or SNP-based platforms. CNV, copy number variation; SNV, single nucleotide variation; SNP, Single nucleotide polymorphism; LOM, loss of methylation; GOM, gain of methylation.

<sup>1</sup>CNV status may be determined simultaneously with methylation testing

<sup>2</sup>refer to text for indications for testing

<sup>3</sup>del(11)(p15.5)mat may be detected with lower frequency

**Table 1**

## Clinical features of Beckwith–Wiedemann Spectrum

Cardinal features (2 points per feature)	Suggestive features (1 point per feature)
Macroglossia	Birth weight >2 SDS above the mean
Exomphalos	Facial naevus simplex
Lateralised overgrowth	Polyhydramnios and/or Placentomegaly
Multifocal and/or bilateral Wilms tumour or nephroblastomatosis	Ear creases and/or pits
Hyperinsulinism (lasting beyond one week and requiring escalated treatment)	Transient hypoglycaemia (lasting less than a week)
Pathology findings: adrenal cortex cytomegaly, placental mesenchymal dysplasia or pancreatic adenomatosis	Typical BWSp tumours (neuroblastoma, rhabdomyosarcoma, unilateral Wilms tumour, hepatoblastoma, adrenocortical carcinoma or pheochromocytoma)
-	Nephromegaly and/or Hepatomegaly
-	Umbilical hernia and/or diastasis recti

SDS, standard deviation score. For a clinical diagnosis of classical BWS, a patient requires a score of  $\geq 4$  (this clinical diagnosis does not require the molecular confirmation of an 11p15 anomaly). Patients with a score of  $\geq 2$  (including those with classical BWS with a score of  $\geq 4$ ) merit genetic testing for investigation and diagnosis of BWS. Patients with a score of  $< 2$  do not meet the criteria for genetic testing. Patients with a score of  $\geq 2$  with negative genetic testing should be considered for an alternative diagnosis and/or referral to a BWS expert for further evaluation.

**Table 2**

Summary of BWSp molecular defect categories and recurrence risk

Molecular defect	Frequency of molecular defect	Mosaicism observed	Risk of recurrence	Characteristic clinical features (compared with other molecular subgroups)
IC1 GOM	5% <sup>48</sup>	Yes <sup>26,54,76,78,81</sup>	<ul style="list-style-type: none"> <li>If no genetic anomaly is present, &lt;1%<sup>28</sup></li> <li>If genetic anomaly (for example, pathogenic SNV of copy number variant in the DMR) is present, 50%; dependent on parental origin<sup>71,73,105,106</sup></li> </ul>	<ul style="list-style-type: none"> <li>Low frequency of exomphalos<sup>10,13,16</sup></li> <li>High risk of Wilms tumour<sup>13,58,149</sup></li> </ul>
IC2 LOM	50% <sup>48</sup>	Yes <sup>26,54,76,78,81</sup>	<ul style="list-style-type: none"> <li>If no genetic anomaly is identified, &lt;1%<sup>28</sup></li> <li>If a <i>cis</i>-acting genetic anomaly is present, 50%; dependent on parental origin<sup>99–103</sup></li> </ul>	<ul style="list-style-type: none"> <li>High frequency of exomphalos<sup>10,13,16</sup></li> <li>Low risk of Wilms tumour<sup>13,58,149</sup></li> </ul>
upd(11)pat	20% <sup>48</sup> (see also paternal uniploidy)	Yes <sup>26,54,61,76,78,81</sup>	<1% <sup>28</sup>	<ul style="list-style-type: none"> <li>High incidence of lateralised overgrowth<sup>10,13</sup></li> <li>Low frequency of exomphalos<sup>10,13,16</sup></li> <li>High risk of Wilms tumour and hepatoblastoma<sup>13,58,149</sup></li> </ul>
Loss-of-function <i>CDKN1C</i> variants	5% (40% in familial cases) <sup>48</sup>	Usually no, but has been reported rarely <sup>83</sup>	50% on maternal transmission <sup>82,83</sup>	<ul style="list-style-type: none"> <li>High frequency of exomphalos<sup>10,13,16</sup></li> <li>Low risk of Wilms tumour<sup>13,58,149</sup></li> </ul>
Dup(11)(p15.5)pat	~2–4% <sup>55</sup>	No <sup>55</sup>	<ul style="list-style-type: none"> <li>50% on paternal transmission<sup>55,94</sup></li> <li>Risk for SRS on maternal transmission<sup>57,95,96</sup></li> </ul>	
Deletions involving 11p15	1–5% <sup>55,98</sup>	No <sup>55</sup>	Dependent on extent and position of CNV, and parent of origin <sup>55</sup>	
Mosaic paternal unidiploidy (Genomewide paternal UPD)	Up to 10% of upd(11)pat <sup>62–67,184</sup>	Yes <sup>62–67,184</sup>	Low <sup>62–67,184</sup>	High frequency of neoplasia <sup>63,64,137,152</sup>
MLID	33% of IC2 LOM cases <sup>75–78,88</sup>	Yes <sup>78,88–91</sup>	Low, unless an <i>in trans</i> genetic variant is identified <sup>79,80</sup>	Unclear <sup>75,76,78,89,92,93</sup>

**Table 3**

Proposed tumour surveillance protocol for Beckwith–Wiedemann spectrum

Tumour risk (% of patients)	Tumour type for surveillance	Surveillance procedures	Timing	Refs column
<b>IC2 LOM</b>				
<ul style="list-style-type: none"> <li>Overall risk (2.6%)</li> <li>Hepatoblastoma (0.7%)</li> <li>Rhabdomyosarcoma (0.5%)</li> <li>Neuroblastoma (0.5%)</li> <li>Thyroid cancer (0.3%)</li> <li>Wilms tumour (0.2%)</li> <li>Melanoma (0.1%)</li> </ul>	Tumour incidence lower than other molecular subgroups; extremely variable tumour spectrum; only half of tumours arise in the abdomen	<ul style="list-style-type: none"> <li>No routine ultrasound scan (USS) surveillance</li> <li>Clinical assessment and USS in response to signs/symptoms or parental concerns</li> </ul>		13
<b>ICI GOM</b>				
<ul style="list-style-type: none"> <li>Overall risk (28.1%)</li> <li>Wilms tumour (24%)</li> <li>Neuroblastoma (0.7%)</li> <li>Pancreatoblastoma (0.7%)</li> </ul>	Wilms tumour	Abdominal USS	Every 3 months from diagnosis until age 7 years	13
<b>upd(11)pat</b>				
<ul style="list-style-type: none"> <li>Overall risk (16%)</li> <li>Wilms tumour (7.9%)</li> <li>Hepatoblastoma (3.5%)</li> <li>Neuroblastoma (1.4%)</li> <li>Adrenocortical carcinoma (1.1%)</li> <li>Phaeochromocytoma (0.8%)</li> <li>Lymphoblastic leukaemia (0.5%)</li> <li>Pancreatoblastoma (0.3%)</li> <li>Haemangiotheloma (0.3%)</li> <li>Rhabdomyosarcoma (0.3%)</li> </ul>	<ul style="list-style-type: none"> <li>Wilms tumour</li> <li>Hepatoblastoma</li> <li>Adrenal tumours</li> </ul>	Abdominal USS	Every 3 months from diagnosis until age 7 years <sup>^</sup>	
<b>CDKN1C mutation</b>				
<ul style="list-style-type: none"> <li>Overall risk (6.9%)</li> <li>Wilms tumour (1.4%)</li> <li>Neuroblastoma (4.2%)</li> <li>Acute lymphatic leukaemia (1.4%)</li> </ul>	Neuroblastoma	Abdominal USS	Every 3 months from diagnosis until age 7 years	13
<b>Classical BWS with negative molecular tests</b>				
<ul style="list-style-type: none"> <li>Overall risk (6.2%)</li> <li>Wilms tumour (4.1%)</li> <li>Neuroblastoma (0.6%)</li> </ul>	Wilms tumour	Abdominal USS	Every 3 months from diagnosis	

Tumour risk (% of patients)	Tumour type for surveillance	Surveillance procedures	Timing	Refs column
<ul style="list-style-type: none"> <li>• Hepatoblastoma (0.3%)</li> <li>• Rhabdomyosarcoma (0.3%)</li> <li>• Adrenocortical carcinoma (0.3%)</li> </ul>			until age 7 years	

Proposed tumour surveillance protocol for patients with Beckwith–Wiedemann spectrum disorder (BWS<sub>p</sub>; including those with isolated lateralized overgrowth who have 11p15 abnormalities) are shown, stratified according molecular subtype. Although there are differences in tumour risks and prevalent tumour types between molecular subgroups when surveillance is recommended, a single surveillance programme is used to reduce confusion and enhance consistency. In specific healthcare systems, practice might currently vary from this protocol (see the text for details).

\* Tumour and histotype prevalence from Maas *et al.*<sup>13</sup> and Mussa *et al.*<sup>16</sup>.

<sup>^</sup> 7 years refers to the risk of Wilms tumour, as Hepatoblastoma usually occurs before age 2 years.

TABLE 4

Consensus recommendations of the clinical working group

R	Recommendation	Strength of recommendation
<i>BWSp scoring system and clinical indications for molecular testing for BWS</i>		
1	Beckwith–Wiedemann spectrum (BWSp) is usually caused by dysregulation of the chromosome 11p15 imprinted region and involves overgrowth in multiple tissues, often in a mosaic state. BWSp encompasses a range of phenotypes and children might present with one or more features (summarised in TABLE 1). Classical Beckwith–Wiedemann syndrome (BWS) and lateralized overgrowth ('hemihypertrophy/hemihyperplasia') are considered subsets of the BWSp (FIG. 1). A third subset is defined as patients with an 11p15 anomaly who do not fit into these first two groups.	A+++
2	There have been many proposed systems to define classical BWS, which have suggested combinations of macroglossia, omphalocele/exomphalos and/or (asymmetric) overgrowth. Although often associated, increased height and/or weight ('macrosomia') is no longer considered a cardinal feature of BWS. For simplicity and consistency, we have developed consensus criteria (TABLE 1); a score of 4 must be reached for a diagnosis of classical BWS. Children who meet these criteria would be considered to have BWSp, even if an 11p15 anomaly is not identified.	A+++
3	BWSp lateralized overgrowth is defined as a marked increase in the length and/or girth of most or all of one side of the body compared to its contralateral side, with an 11p15 abnormality. A child with an 11p15 anomaly who does not meet the criteria for classical BWS or BWSp lateralized overgrowth is still considered to be part of the BWSp. There is currently insufficient data to determine the management guidelines for patients with LO without an identified 11p15 anomaly in tested samples; this group falls outside the scope of this consensus.	A+++
4	We recommend molecular testing in anyone suspected of being in the BWSp (lateralized overgrowth, classical BWS or features in TABLE 1). For simplicity, we would recommend molecular testing for any patient with 2 points. In cases where isolated omphalocele and/or exomphalos is present, testing can be considered at the discretion of the physician. Testing is also recommended with a family history when a parent has a heritable pathogenic 11p15 anomaly, which places the child at a 50% risk of being affected. First tier testing is blood lymphocytes.	A+++
5	Hypoglycemia is defined as plasma glucose levels <50 mg/dL for the first 6 hours of life and <60 mg/dL thereafter. Hyperinsulinism is defined as a glucose infusion rate of 8 mg/kg/min, a detectable level of insulin and/or C-peptide and undetectable levels of ketones and free fatty acids. Transient hypoglycaemia as a suggestive feature is defined by the above criteria lasting less than a week. Hyperinsulinism as a cardinal feature is defined by these criteria lasting beyond one week and/or requiring escalated treatment.	A++
<i>BWS and assisted reproduction technology (ART)</i>		
6	There is an established association between ART and BWS. The absolute risk of BWS in an individual conceived by ART is estimated to be very low (no more than 1 in 1,000). Additional research is required to further characterize this association and the relationship between subfertility, hormonal stimulation, embryo manipulation and imprinting defects.	A+++



TABLE 5

Consensus recommendations of the molecular working group

R	Recommendation	Strength of recommendation
<i>Molecular genetic analysis</i>		
7	Molecular genetic testing should be performed by a health professional experienced in the field of imprinting disorders. Recommended nomenclature (e.g. HGVS) should be adopted in publications and in test reporting	A+++
8	The flowchart outlined in FIGURE 3 should be followed for molecular diagnosis of BWSp.	A+++
9	First-line molecular testing should include DNA methylation analysis of the <i>H19/IGF2:IG</i> DMR (IC1) and <i>KCNQ1OT1:TSS</i> DMR (IC2). If a DNA methylation defect at either or both DMRs is found, further tests should be performed to identify possible underlying CNV or upd(11)(p15.5)pat (if it was not discriminated in initial diagnostic testing).	A+++
10	Given the different tumour spectrum associated with mosaic paternal uniparental diploidy, further testing should be considered to distinguish this condition from upd(11)(p15.5)pat.	A+++
11	Detailed analysis of the <i>H19/IGF2:IG</i> DMR should be considered in individuals with GOM of this region, as SNVs and/or small CNVs can occur in these cases and confer high risk of recurrence (prioritized in the presence of a positive family history).	A+++
12	In cases with a negative methylation test result, second-line molecular testing should be considered, and might include sequencing of the coding exons and the exon–intron boundaries of <i>CDKN1C</i> (prioritized in the presence of a positive family history, cleft palate or abdominal wall defect (umbilical hernia or exomphalos))	A+++
13	In cases with a negative methylation test result, second-line molecular testing should be considered, and might include analysis of additional tissues to detect somatic mosaicism (prioritized in the presence of asymmetric overgrowth).	A+++
14	In cases with a negative methylation test result, second-line molecular testing should be considered and might include further tests for rare chromosomal rearrangements	A+++
15	In cases with a negative methylation test result, second-line molecular testing should be considered, and might include re- evaluation of the clinical diagnosis and reconsideration of differential diagnoses.	A+++
16	Genetic counselling should be performed by a health professional experienced in the field of imprinting disorders.	A+++
17	As the recurrence risk associated with genetic defects (for example, <i>CDKN1C</i> loss of function variants, CNVs and DMR SNVs) is dependent on their size, location and parental origin, these factors should be taken into consideration during counselling for the family.	A+++
<i>Prenatal molecular genetic analysis</i>		
18	Prenatal molecular diagnostic investigations should be considered if prenatal ultrasonography reveals potential features of BWSp and lead to a specific diagnosis (or exclude other potential conditions); or if positive family history with a known molecular defect is present, which would influence the management of the relevant pregnancy.	A+++
19	The flowchart indicated for postnatal testing (FIG. 3) is not necessarily applicable to prenatal testing. Modification of this flowchart depends on the individual setting (for example, known molecular defects and specific clinical features).	A+++
20	Prior to offering prenatal diagnosis for BWSp, a detailed discussion of the technological limitations and ethical issues should be undertaken with the parents; in particular, they should be made aware that a normal result does not necessarily exclude the diagnosis.	A+++
21	It is recommended that centres offering prenatal diagnosis prospectively collect information on the true/false positive/negative diagnostic rates and that this information is contributed to multicentre audits to enable best practice guidelines to be further developed and refined.	A+++

upd(11)(p15.5)pat, segmental paternal uniparental isodisomy of 11p15.5;

TABLE 6

## Recommendations of the management working group

R	Recommendation	Strength of recommendation
22	It is recommended that each patient with BWSp should have an experienced lead healthcare provider who will organise the referral to each specialist, and will coordinate care for the patient.	A+++
<b>Prenatal management</b>		
23	If a diagnosis of BWSp is suspected or confirmed in the prenatal period, then potential BWSp-related foetal and maternal complications (for example, foetal congenital anomalies, shoulder dystocia from macrosomia, postnatal hypoglycaemia and maternal preeclampsia) should be anticipated and appropriate clinical care should be performed.	A+++
24	If a diagnosis of BWSp is suspected or confirmed in the prenatal period, then delivery should take place in a clinical facility where neonatal intensive care can be provided.	A+++
<b>Growth and lateralised overgrowth</b>		
25	Growth charts from BWSp patients are needed.	A+++
26	Physicians should be aware of the rare possibility of final height >2 SDS above the mean. Postnatal growth and pubertal development should be monitored at least annually until the end of growth.	A++
27	Appropriate interventions might be proposed in case of possible tall stature with the same procedures as for other patients with tall stature.	A++
28	Monitoring of leg length discrepancy should be based on clinical examination.	A++ (LO)
29	Patients with BWSp should be monitored for leg length discrepancy at least annually during childhood and referred to a paediatric orthopaedic surgeon if present.	A+++ (LO)
30	Shoe-lifts might be indicated for LLD <2 cm. Epiphysiodesis is usually indicated for predicted LLD >2 cm. Reversible epiphysiodesis might be preferred.	A++ (LO)
31	Lengthening of the shorter normal limb should be considered only for specific cases.	A+++ (LO)
32	Surgical correction of upper limbs asymmetric overgrowth is generally not indicated.	A+++ (LO)
<b>Management of macroglossia</b>		
33	If significant airway obstruction is suspected, a careful evaluation including sleep studies (polysomnography) and/or pulmonologist consultation and ENT consultation should be performed.	A+++
34	Tongue reduction surgery should be considered usually after the age of 1 year if there are macroglossia-associated feeding problems, persistent drooling, speech difficulties, dental malocclusion and psychosocial problems caused by the altered appearance.	A+++
35	Surgical intervention (adenoid tonsillectomy ± tongue reduction surgery) should be considered earlier in cases of severe airway obstruction.	A+++
36	In cases of feeding difficulties, support from a feeding specialist and dietetics should be proposed.	A+++
37	Tongue reduction surgery should be performed by an experienced surgical team after detailed assessment by a multidisciplinary team (including paediatric anaesthesiologist, intensive care unit, surgeon, speech therapist and orthodontist) preferably in a reference centre.	A+++
38	The results of surgery should be carefully audited and postoperative follow-up should continue until age 16 years.	A+++
<b>Management of exomphalos</b>		
39	Treatment of exomphalos in the context of BWSp should be in accordance with general recommendations for the treatment of exomphalos; however, in BWSp-associated cases, attention should be paid to the risk of hypoglycaemia and the anaesthetic risks associated with severe macroglossia.	A+++
<b>Management of hypoglycaemia</b>		
40	Capillary blood glucose should be monitored in neonates with a clinical suspicion or confirmed diagnosis of BWSp for the first 48 hours of life. Hypoglycaemia should be defined by two consecutive (30 minutes) glucose levels <50 mg/dl (2.75 mmol/l) during the 6 first hours of life or <60 mg/dl (<3.5 mmol/l) later. In case of hypoglycemia, the newborn should be transferred to a neonatal intensive care unit.	A++

R	Recommendation	Strength of recommendation
41	A diagnostic fasting test (including measurement of glucose, insulin and ketones after 6 hours of fasting for full-term babies, and after 4 hours for preterm babies) should be performed for neonates with a suspicion of BWSp 48 hours after birth and before discharge from the nursery.	A++
42	No specific management of hyperinsulinism and/or hypoglycaemia has been proposed in the context of BWSp and management of hyperinsulinism and/or hypoglycaemia should be performed according to general recommendations.	A++
43	In case of severe persistent hyperinsulinism in a patient with BWSp, additional causes of hyperinsulinism should be investigated.	A+++
<b>Management of cardiac lesions</b>		
44	Physicians should be aware of the increased prevalence of cardiac anomalies in children with BWSp.	A++
45	A baseline, clinical cardiovascular examination should be performed at diagnosis in all children with clinical/molecular diagnosis of BWSp. Individuals with clinically detected or suspected cardiovascular abnormalities should be referred for specialist cardiac assessment and echocardiography.	A+++
46	Annual evaluation and electrocardiogram are recommended in patients with genomic rearrangements involving the IC2 ( <i>KCNQ1OT1</i> :TSS DMR) region.	B+
47	Management and follow-up of congenital cardiac lesions (for example, ventricular septal defect (VSD), <i>et cetera.</i> ) should be as in the population without BWSp.	A+++
<b>Management of neurological features</b>		
48	Cognitive development should be monitored by the paediatrician. Particular attention should be paid to those with risk factors such as preterm birth, neonatal hypoglycaemia, and carriers of chromosome rearrangements or paternal genome-wide UPD.	A+++
49	For patients with a clinical diagnosis of BWSp and a learning disability with no molecular or chromosomal anomaly, other potential diagnoses should be considered and excluded (Supplementary TABLE 2)	A+++
50	Neurological investigations, including MRI, might be indicated only in children with neurological symptoms.	A++
<b>Management of renal complications</b>		
51	At diagnosis of BWSp, all patients should be screened for nephrourological malformations by clinical evaluation and ultrasound scan (USS).	A+++
52	Physicians should be aware of the possibility of hypercalciuria, which can lead to nephrocalcinosis.	A++
53	Patients with ultrasound scan (USS)-detected anomalies should be referred to a paediatric nephrologist and urologist for specific follow-up.	A+++
54	For patients undergoing abdominal surveillance for tumour screening, physicians and radiologists should pay attention to the possibility of nephrocalcinosis and/or stones.	A+++
55	For patients with BWSp, at the time of adult transition, a nephro urological evaluation (clinical examination, blood pressure and USS) should be performed.	A++
<b>BWSp and embryonal tumours</b>		
56	Screening should be stratified according to the genotype.	A+++
57	Abdominal ultrasound scan (USS) for BWSp-related tumours every 3 months until the 7th birthday is recommended for all patients with BWSp, except patients with isolated IC2 LOM.	A++
58	For patients with BWSp and upd(11)pat, abdominal ultrasound scan (USS) for Wilms tumour and hepatoblastoma every 3 months until age 7 years is recommended.	A+++
59	For patients with BWSp and IC1 GOM ( <i>H19/IGF2:IG</i> DMR), abdominal ultrasound scan (USS) for Wilms tumour every 3 months until age 7 years is recommended.	A+++
60	For patients with BWSp and IC2 LOM ( <i>KCNQ1OT1</i> :TSS DMR), no tumour surveillance is recommended.	* A/B+
61	For patients with BWSp and a <i>CDKN1C</i> mutation, abdominal ultrasound scan (USS) for neuroblastoma every 3 months until age 7 years is recommended.	A+
62	For patients with BWSp and a 11p15 duplication, abdominal ultrasound scan (USS) for Wilms tumour every 3 months until age 7 years is recommended.	A+++

<b>R</b>	<b>Recommendation</b>	<b>Strength of recommendation</b>
63	For patients with classical BWS without a molecular defect, abdominal ultrasound scan (USS) every 3 months until age 7 years is recommended.	A++
64	α-fetoprotein (αFP) screening is not recommended for patients with BWSp	A+
65	Catecholamine screening is not recommended for patients with BWSp	A+++
66	There should be a lower threshold for investigation in cases of possible tumour-related symptoms or in response to parental concerns.	A+++
67	Treatment of tumours in patients with BWSp might be different from treatment of patients with sporadic diseases and should be discussed with respective study groups unless specific BWSp recommendations are given in the relevant tumour treatment protocols.	A+++
<b><i>Late-onset complications</i></b>		
68	Individuals with BWSp should be reviewed at the age of 16–18 years to identify any complications that will require continued follow-up by adult healthcare services.	A+++
69	Young adults with BWSp should be alerted to the availability of genetic counselling so that they can seek advice prior to starting a family.	A+++
70	Given the paucity of data on the long-term health effects of a diagnosis of BWSp, further research should be undertaken.	A+++
<b><i>Psychological and counselling aspects</i></b>		
71	Health professionals caring for children and families with BWSp should take a holistic approach to care and be prepared to offer referral to specialist counselling and family support services as required. Especially, psychological evaluation and support should be offered to children and their families if required.	A+++
72	When the clinical diagnosis is confirmed, parents should be offered A+++ the contact details of BWSp support groups.	

\* Equal numbers of participants chose option A and option B