REVISED VERSION

Clinical and Molecular Diagnosis, Screening and Management of Beckwith-Wiedemann syndrome: An International Consensus Statement

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Abstract

The human genomic imprinting Beckwith-Wiedemann syndrome(BWS) is characterised by phenotypic variability that may include macroglossia, anterior abdominal wall defects, pre- and/or postnatal overgrowth, neonatal hypoglycaemia, lateralised overgrowth and embryonal tumour predisposition. The genetics of BWS is complex but most cases have a molecular abnormality altering expression/function of the chromosome 11p15.5 imprinted gene cluster products (particular IGF2 and CDKN1C). Delineation of the molecular defect can predict familial recurrence risks and risk/type of embryonal tumour. Despite recent advances in knowledge there is marked heterogeneity in clinical diagnostic criteria and care. To enhance BWS diagnosis, investigation and management, an international consensus group agreed 72 recommendations for clinical and molecular diagnosis and management and a definition of the BWS spectrum (BWSp) covering classical BWS without a molecular diagnosis and BWS-related phenotypes (including isolated lateralised overgrowth) with an 11p15.5 molecular anomaly. The consensus recommendations apply to patients with BWSp and include comprehensive protocols for the molecular investigation, care and treatment from the prenatal period to adulthood. The consensus agreed to recommend a tumour surveillance programme targeted by molecular subgroups as favoured in some European centres but it is recognised that surveillance might differ according to the local health care system (e.g. in the United States) and it is important that the results of targeted and universal surveillance are evaluated prospectively. Given that BWSp is a rare disorder, international collaboration, including prospective audit of the results of implementing the consensus recommendations, is required in order to expand the evidence base for the design of optimum care pathways.

Introduction

Beckwith-Wiedemann syndrome (BWS) is a multisystem human imprinting disorder with variable clinical expression and complex molecular aetiology[1]. BWS may present prenatally or in adult life but is most commonly diagnosed in the neonatal period or in early childhood with an estimated prevalence of 1:10 340 live births[2]. Since the first descriptions half a century ago, more than 1500 BWS-related articles have been published, but there is variable practice regarding the diagnosis and care for individuals with BWS. To address these issues the COST-funded European Network for Congenital Imprinting Disorders (www.imprinting-disorders.eu) initiated a BWS Consensus Programme that involved extensive literature review, preparation and critical appraisal of draft documents and a final face-to-face consensus meeting of invited experts and patient group representatives. This produced a series of recommendations for the diagnosis and care for individuals with the newly defined Beckwith-Wiedemann spectrum (BWSp).

Methods

The International BWS Consensus Group comprised 41 participants from 36 institutions from 11 countries with expertise in aspects of BWS. Participants included clinicians, clinical and research scientists and patient group representatives, the majority based in Europe. A modified Delphi consensus process was adopted. 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, and a plenary 3-day meeting of 35 participants (including two patient group representatives) in March 2017 to discuss the draft consensus documents, formulate and vote on the consensus recommendations (see Text Box 1). This consensus statement summarises the outcome of these discussions and is divided into three subject area: clinical aspects, molecular aspects and care and management.

Working Group Topics: Background and Recommendations

1. Clinical Aspects of BWS

Since the seminal descriptions by Beckwith[3] and Wiedemann[4] there have been many attempts to define BWS using various clinical criteria (see Supplemental Table 1) but no agreed definition had emerged. Since the findings of molecular abnormalities of 11p15 in BWS[5–7] it has been recognised that the genetic and epigenetic changes are frequently mosaic and lead to a range of phenotypes. These include "classical BWS" (OMIM #130650) characterised by macroglossia, anterior abdominal wall defect and pre- and postnatal overgrowth etc. (see Supplementary Table 1), but also some cases of isolated lateralised overgrowth (previously called "isolated hemihypertophy/hemihyperplasia" OMIM #235000)[8] and also patients with an 11p15 molecular anomaly who do not fit into these first two groups, termed "atypical BWS". Given the overlapping phenotypes and common molecular mechanisms, the consensus decided that these phenotype/genotype combinations could be best classified as parts of the BWS spectrum (BWSp) (**R1**) and that the recommendations of this consensus should be applied to individuals with BWSp (see Figure 1 and Text Box 2).

1.1 Clinical features of Beckwith-Wiedemann spectrum

Classically BWS has been described by macroglossia, macrosomia, abdominal wall defects, and an increased risk for embryonal tumours. There is growing recognition that not all patients with BWS display all of these phenotypic features and that patients have gone undiagnosed because they are missing one of these features such as macrosomia[9,10].The clinical features outlined as part of the BWSp scoring system include features 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. Lateralized overgrowth is the novel term for hemihypertrophy/hemihyperplasia, which is defined as asymmetric overgrowth of part of the body[8]. Embryonal tumours such as Wilms tumours (WT) and hepatoblastoma can occur outside of the scope of BWSp, however multifocal WT are more likely to occur in BWSp. Hyperinsulinism as cardinal feature is defined as prolonged hypoglycaemia in the context of elevated insulin levels lasting beyond one week and/or requiring escalated treatment[11]. Transient hypoglycaemia resolves without the need for further intervention. Pathology findings cannot always be evaluated, however the diagnosis of BWSp should be considered in cases of adrenal cortex cytomegaly, placental mesenchymal dysplasia, and pancreatic adenomatosis.

Additionally, if samples are available, especially from the placenta after birth and the diagnosis is being considered, pathologic 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 therefore are given less weight in the scoring system outlined below. Suggestive Features include birth weight greater >+2SD, facial naevus flammeus, polyhydramnios or placentomegaly, ear creases or pits, transient hypoglycaemia, embryonal tumours, nephromegaly or hepatomegaly, and umbilical hernias or diastasis recti. Macrosomia has been defined differently in different clinical cohorts making it challenging to assess the role it has as a primary feature.

1.2 Consensus Beckwith-Wiedemann Spectrum Scoring System and Clinical Definition (R1-R5; Text Box 2)

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 [12–16])) with an aim to optimise the likelihood of a classical and molecularly confirmed diagnosis. Frequently cited and recent phenotype papers were reviewed for the prevalence of individual clinical features (see **Supplementary Table 1**) and these were then classified as cardinal or suggestive (**Table 1**), several papers referenced the same patient cohorts so data was abstracted from the nine papers of these papers that contained the cohorts.[17–23] The goal of this scoring system was to recognise that BWS falls into a clinical spectrum and that some features long considered to be classically part of the syndrome are not present in every patient and therefore the diagnosis should not be dismissed due to the absence of that feature. Additionally, this consensus sought to include elements that could be pathognomonic for BWS. It was also determined that the same system could be used to both provide guidance regarding when to pursue genetic testing in addition to when a diagnosis of classical BWS was present. We assessed this new system in comparison to previously published systems (Supplementary Figure 1) keeping in mind that previous systems focused on the diagnosis of classical BWS and molecularly confirmed BWS not in diagnosis of the BWSp.

Cardinal Features are considered key to the clinical diagnosis while *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[12] and demonstrated to be largely superior to previous diagnostic systems (Supp Fig 1) with the limitation that transient hypoglycaemia versus prolonged hyperinsulinism were not typically distinguished in the prior cohorts so this feature could not be assessed and that macrosomia was variably defined in previous cohorts.

Cardinal Features include macroglossia, exomphalos, lateralized overgrowth, multifocal Wilms

tumour, prolonged hyperinsulinism, and distinct pathologic findings unique to BWS. The major differences between the consensus and previous scoring systems are the classification of macrosomia and hyperinsulinism. Although often associated, macrosomia (height and/or weight >2SD) is no longer considered a cardinal feature as it is variably defined in previous cohorts and it may only be present in about half of BWS patients.[21,23] Hyperinsulinism (defined in **R5; Text Box 2**) without another identifiable molecular cause can be the initial presenting feature of BWSp.[24,25] Hyperinsulinism is classed 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 these features (see Table 1). For a clinical diagnosis of classical BWS, a patient needs a score of 4 or more based on Cardinal and Suggestive features (Table 1, **R2**), this clinical diagnosis does not require the molecular confirmation of an 11p15 anomaly. Patients with a score of 2 or more based on Table 1 merit genetic testing per the algorithm in Figure 3. Patients with a score of less than 2 do not meet criteria for genetic testing. Patients with a score of 2 or more with negative testing should be considered for an alternative diagnosis and/or whether they should be referred 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 <4 and no molecular abnormality. That being said, patients with a cardinal feature of BWS such as macroglossia, hyperinsulinism, a multifocal WT, or a pathological finding, should be referred to a specialist with expertise in BWS for further evaluation. Cases with isolated exomphalos are more common and are less likely to have an 11p15 defect and therefore not be included in the BWSp. Lateralized overgrowth (LO) can occur as a feature of BWSp and independent of BWSp[8]. When LO occurs with an 11p15 abnormality it is considered part of BWSp. There are multiple molecular causes of LO aside from 11p anomalies and LO 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 so that recommendations for further investigation and clinical management were not made (**R3**).

1.3 Clinical indications for molecular testing of BWSp

The consensus recommended that molecular testing is indicated in cases with a score of 2 or more (see Table 1) unless there is an alternative explanation (e.g. maternal diabetes for macrosomia) (**R4**). For isolated exomphalos, testing is discretionary. Testing is recommended in cases with a family history and a known heritable pathogenic 11p15 anomaly (a positive family history may occur in 10-

15% of patients).[26,27] Some features included in some previous diagnostic criteria (e.g. cleft palate, advanced bone age, polydactyly, and supernumerary nipples) are suggestive of an alternative diagnosis such as Simpson-Golabi-Behmel syndrome and not included in the consensus scoring system. Though renal abnormalities are common in 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 (Figure 3, **Supplementary Table 2)**.

1.4 BWS and Assisted Reproduction Technology (ART) (R6; Text Box 2)

Assisted reproductive technologies (ART) are defined as treatments handling both gametes outside the body, and include procedures such as in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). ART account for 1-3% of all births in industrialized countries. These techniques are regarded as safe, but it has been suggested that the establishment and/or maintenance of DNA methylation at imprinted loci may be disturbed by ART. Following reports of children with a rare molecular subtype of Angelman syndrome born after ICSI [28,29] and an increased frequency (approximately 4-6-fold) of ART births in children with BWS[30–32], a population-based survey estimated the risk of BWS in their IVF-conceived children to be ~1/4,000, substantially greater than in the general population.[33] A recent study found a 10-fold increased risk of BWS with ART but an absolute risk of ~1/1000.[34] Though some epidemiological studies have not detected an increased relative risk of BWS in children born after ART [35,36], molecular studies support an association as >90% of children with BWS conceived by ART have an epimutation at the centromeric imprinting centre (IC2, KCNQ1OT1 TSS-DMR) compared to ~50% of non-ART children with BWS.[37] Various factors might contribute to an association between ART and AS/BWS including infertility *per se* [38,39] superovulation or *in vitro* embryo culture [40–42]. Large offspring syndrome (an ART associated phenomenon in sheep and cows that has some phenotypic similarity to BWS) has been reported to be associated with epigenetic alterations similar to those observed in BWS.[43]

2. 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 (see Figure 2). Each domain harbours its own imprinting control region (marked by a differentially methylated region (DMR)). The growth factor gene *IGF2* and the gene encoding the non-translated long non-coding RNA *H19* are located in the telomeric domain and controlled by the *H19/IGF2*:IG DMR (OMIM *616186; also known as ICR1, *H19*-DMR or Imprinting Centre 1

(IC1)). The cell cycle inhibitor gene *CDKN1C* and the gene encoding the regulatory long non-coding RNA *KCNQ1OT1* are located in the centromeric domain and controlled by the *KCNQ1OT1*:TSS DMR (OMIM *604115; also known as KvDMR, *LIT1* DMR, ICR2 or Imprinting Centre 2 (IC2)). The HGVS-recommended nomenclature, *H19/IGF2*:IG DMR and *KCNQ1OT1*:TSS DMR should be adopted in publications and test reporting[44] (**R7**) but for brevity IC1 and IC2 are used hereafter.

A molecular defect affecting imprinted genes in 11p15 can be demonstrated in ~80% of patients with BWSp[26]. DNA methylation abnormalities are the most frequent defects; loss of methylation (LOM) at the maternal IC2 allele is found in ~50% and gain of methylation (GOM) at the maternal IC1 allele in 5-10% of the cases.[45] Mosaic and segmental paternal uniparental isodisomy of 11p15.5 (segmental upd(11)pat) can be detected in 20% of cases, intragenic *CDKN1C* mutations in 5% of sporadic and 40% of familial cases, and chromosomal abnormalities in 11p15 in <5%. A molecular diagnosis is not reached in up to 20% of patients[26]. 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 (i.e. one affected and one unaffected by BWSp).[46,47] Because of circulation sharing during development, DNA from blood cells or saliva may 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. Therefore, buccal swab is the preferred source of DNA for unambiguous diagnosis in cases of discordant monozygotic twins.

2.1 Molecular Genetic Testing for BWSp (see Text Box 3; R7-R21)

A chart summarising the molecular diagnostic pathway for investigation of suspected BWSp is presented in Figure 3 (**R8**).

First line molecular testing procedures should assay IC1 and IC2 methylation. This is abnormal in case of IC2 LOM, IC1 GOM, CNVs and segmental upd(11)pat (both IC2 LOM and IC1 GOM).[48] Abnormal methylation status confirms a diagnosis of BWSp, but its underlying mechanism must be established to define management, genetic counselling and recurrence risks.[45,49,50] Hence, if methylation is assayed with a technique that does not estimate DMR copy number, this should then be determined in all cases with IC1 and/or IC2 methylation abnormalities (see Figure 3) **(R9**). Currently methylation-specific (MS) multiplex ligation-dependent probe amplification (MS-MLPA) is the commonest diagnostic test, since it detects simultaneously DMR methylation status and copy number; but other techniques (including such as MS-PCR and MS-qPCR) are more sensitive in cases with low-level mosaicism (for a detailed list, see refs[48,51–53]).

2.2 Investigations to be performed if a molecular diagnosis for methylation abnormalities is

positive

If a DMR copy number variation (CNV) is implied by a PCR based methodology such as MLPA) then chromosome microarray (CMA) analysis (such as oligonucleotide- or SNP (single nucleotide polymorphism)-based arrays) should be considered to determine the nature and extent of the deletion/duplication and karyotype/FISH/subtelomeric MLPA should be considered to identify possible translocations.[53–56] Testing can then be extended to other family members as appropriate. A SNP-based array will also allow detection of upd(11) (and indeed mosaicism) if a CNV is not detected.

If IC1 GOM and IC2 LOM without evidence of CNV are detected mosaic segmental upd(11)pat is likely and can, if necessary, be confirmed using microsatellite analysis or SNP-based CMA.[49,57,58] SNP-based CMA is considered to be the most sensitive tool to investigate low mosaic (e.g. 1-5%) segmental upd(11)pat.[57] Mosaic paternal unidiploidy (genomewide paternal upd) affects up to 10% of cases with segmental upd(11)pat and, as this is associated with additional clinical features and increased risk for tumour development, further investigations (SNP array/microsatellite markers) to detect this molecular abnormality should be considered [59–65] (**R10**).

Up to 20% of patients with **IC1 GOM** may carry small CNVs in the DMR which cannot be detected by CMA, or single nucleotide variations (SNVs) in OCT4/SOX binding sites; these CNVs and SNVs are associated with a high recurrence risk.[66–72] Some small CNVs can be detected by MS-MLPA, but detection of SNVs would require additional investigations unavailable in most diagnostic laboratories (**R11**). However, targeted IC1 sequencing can be considered in a specialised laboratory if MS-MLPA shows IC1 GOM and no CNV, and especially if there is a family history of BWSp.

IC2 LOM is the most common epigenetic finding in BWSp. IC2 DMR deletions are rare[54], and at present there is no indication for analysing BWSp patients with IC2 LOM for SNVs. Around a third of patients with IC2 LOM may have multi-locus imprinting disturbance (MLID, see 2.4). In most cases the clinical significance of MLID is uncertain and so routine testing for MLID is not usually indicated, but 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 *trans*-acting mutations should be considered.[73]

2.3 Investigations to be performed if first line molecular testing is negative

A negative result for first line IC1 and IC2 methylation testing does not exclude BWSp for a variety of reasons, including (a) low-level mosaicism below the limit of detection of methylation testing, (b) a *CDKN1C* mutation, (c) a rare balanced chromosomal rearrangement (e.g. inversion/translocation),

(d) an unrecognised or undetected cause of BWSp (up to ~20% of patients with a characteristic BWS phenotype remain without a molecular diagnosis) or (e) an incorrect clinical diagnosis (**R12-R15**). Further molecular testing should be prioritised according to the most likely cause. For example, a less severe phenotype with LO would suggest mosaicism, whereas a classical BWS phenotype with an abdominal wall defect and a positive family history would favour a *CDKN1C* mutation.

Mosaicism for the molecular defect occurs in most sporadic cases of BWSp, and different tissues may have different proportions of affected cells. Usually first-line diagnostic testing is performed with blood-leukocyte DNA and IC1/IC2 methylation level may be equivocal or within the normal range. Analysis of DNA from buccal swabs, cultures of fibroblasts or cells of mesenchymal origin, e.g. obtained at the surgery of hyperplastic tissues, improves the detection rate for all mosaic defects[48,48,74](**R13**).

***CDKN1C* mutations** account for ~5% of sporadic cases of BWS and 40% of familial cases, in maternal inheritance.[75] Detection of a candidate pathogenic *CDKN1C* variant enables appropriate family studies to clarify familial recurrence risks.[75,76] De novo mutations may be mosaic.[76]

Rare **maternally inherited balanced translocations/inversions** involving 11p15 may or may not be associated with IC2 methylation anomalies and should be considered if first line testing is negative [77–80] (**R14**).

2.4 Multilocus imprinting disturbance (MLID)

Multi-locus imprinting disturbances (MLID) are those with altered DNA methylation additional to the lesion responsible for the primary clinical presentation.[81] MLID has a higher prevalence in BWSp than in other imprinting disorders, and genome-wide analyses have revealed MLID in about a third of BWSp patients with IC2 LOM, but not in those with segmental upd(11)pat or IC1 GOM.[45,81–89] MLID in BWSp almost exclusively involves loci methylated in the maternal, not the paternal germline, though rare cases show LOM at both IC2 and IC1 (the latter finding is a feature of the growth restriction disorder Silver-Russell syndrome (SRS)).[70,83,90]

Rare cases of BWSp-MLID have been associated with biallelic maternal-effect genetic mutations in *NLRP2* and *NLRP5* [73] and the possibility of an underlying trans-acting genetic mutation should be considered in genetic counselling.

BWSp-MLID is mosaic, suggesting that the epigenetic errors arise post-fertilisation. Perhaps because of the variable methylation alterations, the effect of MLID on clinical phenotype remains unclear [82,83,85,88,90,91] and routine clinical diagnostic testing is not recommended.

2.5 Recurrence risks in different molecular classes of BWSp

It has been reported that up to 10-15% of BWSp cases are familial and most commonly result from *CDKN1C* mutations, chromosome 11p15 abnormalities and genetic alterations within IC1.[26,92] 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 (see Table 2) (**R17**).

Pathogenic *CDKN1C* variations have a 50% recurrence risk with variable expressivity if the mutation is inherited from the mother.[75,76]

In principle, all 11p15 CNVs and balanced translocations have a 50% recurrence risk with parent-of-origin-dependent phenotypes. 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.[93] In some pedigrees, either BWS or SRS has been observed depending upon paternal or maternal transmission of the 11p15 duplication.[47,56,94] Paternal transmission of a duplicated telomeric domain and maternal transmission of a deleted centromeric domain also usually result in BWSp with high recurrence risk.[47,51,95,96] Prediction of phenotype and recurrence risks associated with smaller CNVs within either the telomeric or centromeric domain can be complex, since it depends on their size, genes and regulatory elements involved.[54,97–102]

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.[71,103,104] Rare familial cases of BWSp-MLID may be caused by maternal effect gene mutations (e.g. *NLRP2* or *NLRP5*) and be associated with a very high recurrence risk.

In the cases with other molecular defects, the recurrence risk is generally low (see Table 2).

2.6 Role of prenatal molecular diagnosis in confirmation and exclusion of BWSp (R18-R21)

Prenatal testing is challenging because of the complexity of the molecular findings. Apart from general aspects of molecular testing (range of disturbances, mosaicism, limitations of the applied tests), the reliability and informative value of prenatal test results and ethical issues must be considered prior to sampling.[105]

The major indications for prenatal diagnosis of BWSp are (a) familial cases with a known genetic alteration and a high recurrence risk and (b) cases with no family history in which prenatal foetal ultrasonography has detected possible features of BWSp (usually exomphalos but also macrosomia, hemihypertrophy, organomegaly, and polyhydramnios) (**R18**). In cases of prenatally detected exomphalos a positive diagnosis of BWSp may be reassuring compared to other potential causes.

Though chorionic villus (CVS), amniotic fluid cells (AF) or foetal blood cells (native and cultured) might be used for molecular testing, there is the possibility that cell culture might influence the methylation patterns. In CVS, the methylation pattern at 11p15.5 might be different from that of embryonic tissues [104,106] and/or CVS might not reflect the (epi)genetic constitution of the foetus and false positive results may occur.[105] False-negative prenatal tests may occur with all types of testing because of mosaicism and so a normal prenatal test result cannot absolutely exclude a diagnosis of BWSp (**R20**).

3. Care and Management Aspects (see Text Box 4)

In view of the complex multisystem manifestations of BWSp the consensus recognised the requirement for effective coordination of health care (**R22**).

3.1 Prenatal management

In cases of BWSp for which a risk of recurrence has been identified (see table 2), some parents may wish to consider prenatal diagnosis. If a molecular diagnosis is not available or indicated then ultrasonographic (USS) 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.[107] Rarer manifestations detectable by prenatal USS include placental mesenchymal dysplasia, urinary tract abnormalities, cardiac defects, adrenal cysts and masses.[108,109] Abnormal prenatal biochemical screening results (e.g. elevated first trimester free beta-HCG [107–109] and/or increased α-fetoprotein (αFP) levels in the second trimester (associated with exomphalos)[110] can be associated with BWSp in the foetus. In pregnancies known to be at increased risk of BWSp the presence of a single anomaly (e.g. exomphalos) may 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 will have BWSp[110,111] and ~20% of those with placental mesenchymal dysplasia.[112] As cytogenetic/CMA 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 may be helpful for the parents. For less specific features (e.g. urinary tract abnormalities, cardiac defects) testing for BWSp is likely to depend on whether there are multiple BWSp-related features.

When a prenatal diagnosis of BWSp is suspected or confirmed the management of individual congenital anomalies (e.g. exomphalos, cardiac defect) generally follows standard protocols. However, macrosomia may cause problems (e.g. shoulder dystocia) at delivery and so growth should be carefully monitored in the latter stages of pregnancy and appropriate arrangements for delivery made (**R23, 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 etc. should be anticipated and appropriate monitoring and facilities put in place (see Sections 3.3, 3.5 and 3.6 below) (**R23, R24**).

Maternal complications associated with a diagnosis of foetal BWSp include gestational hypertension (~2.4-fold increased risk) and pre-eclampsia.[113] HELLP syndrome (haemolysis, elevated liver

enzymes and low platelets) has been reported occasionally in BWSp.[114]

3.2 Growth and lateralised overgrowth (LO) (R25-R32)

Pre- and postnatal overgrowth have been considered to be cardinal features in previous reports but overgrowth occurs only in 43%-65% of patients.[115] Overgrowth at birth may be relatively more common in patients with IC1 GOM and segmental pat(11)upd than in other molecular subgroups[17,116]. 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. Little data about final adult height is available but in one study this was increased compared to parental target height (1.7±1.1 SDSs) with about half of the patients >+2SDs [21](**R26**). Advanced bone age is infrequent (~3%) [117,118] and, to date, there is no data regarding treatment of tall stature in cohorts of patients with BWSp (**R27**).

Lateralised Overgrowth

LO may occur in all molecular subtypes of BWS but is rare with a *CDKN1C* mutation and most frequent with segmental upd(11)pat.[12,17] 11p15 molecular abnormalities may be observed in patients with isolated LO enabling a diagnosis of BWSp in such cases.[117,119] Leg length discrepancy (LLD) can be associated with significant morbidity and impact quality of life. The management of LLD will depend on severity. Shoe-lifts may be indicated for LLD less than 2 cm. As in isolated (non-BWSp) LLD, epiphysiodesis may be considered for LLD discrepancy >2cm.[120] (**R30**).

3.3 Management of macroglossia (R33-R38)

90% of children diagnosed with classical BWS have macroglossia and BWSp is the most common cause of macroglossia in childhood.[121]

Though macroglossia may appear to regress spontaneously in some children (from a combination of a decrease in growth velocity and increased growth of the mandible), about 40% may have a surgical tongue reduction.[122] 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 the difficulties with speech, feeding and drooling.[123–125] (**R33-35**).

The enlarged tongue is usually increased in all three dimensions and the aim of surgery is to reduce the tongue bulk but preserve normal shape and improve function. The most common surgical approach is anterior wedge resection but a variety of other techniques have been described.[122,125,126]

Surgical complications, albeit infrequently, can include postoperative oedema of the tongue and wound dehiscence.

Rarely respiratory problems may require surgery to be performed in the neonatal period and preoperative tracheostomy may be required.[122] When obstructive sleep apnoea is suspected, an airway evaluation and appropriate further investigation with polysomnography can be used for objective assessment [127,128] (**R33**). In the absence of respiratory obstruction, surgery is generally delayed until at least age 12 months (when tongue size is more stable) (**R34-34**). If the indication for surgery is unclear then the child's progress should be monitored to see if indications arise in the future. Long-term follow up studies generally show good results in most cases with cosmetic improvement, reduced drooling, resolution of feeding difficulties, improved speech, adequate tongue mobility and, usually, no significant effect on taste sensation.[122,124,125] Surgery has been reported to provide good outcomes in children operated at a wide variety of ages but mainly before age 2-3 years.[122,124]

In order to facilitate objective assessments and 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 (**R37**).

3.4 Management of Exomphalos (R39)

Exomphalos is one of the cardinal features of BWSp (see Table 1) and is preferentially associated with molecular defects occurring within the centromeric domain (i.e. IC2 LOM or *CDKN1C* mutations).[12,17,116] To date, no specific recommendations have been given regarding the management of exomphalos which occur in BWSp patients compared to isolated exomphalos (**R39**).

Molecular investigations of apparently isolated exomphalos in neonates rarely detect an abnormality in the absence of additional BWS features.[129]

3.5 Management of Hypoglycaemia/hyperinsulinism (R40-R43)

Hypoglycaemia in BWSp is due to excess insulin and occurs in 30%-60% of children with BWSp.[12,17,116] Though BWSp-related neonatal hypoglycaemia is often transient and resolves within a few days, in up to 20% it can persist beyond the first week of life and require medical treatments or even pancreatectomy for the most severe cases.[11]

Congenital hyperinsulinism (HI) is a rare condition with a range of causes.[11,130] 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 underwent surgery because of persistence of hypoglycaemia after optimal medication.[24]

Diagnosis: While low plasma glucose concentrations are common during the first 24 hours of life in all newborns, by day 3 plasma glucose concentrations in neonates are similar to older children with a normal range of 3.5-5.5 mmol/l (60-100 mg/dL). Therefore, plasma glucose concentrations that are below this range should be further investigated by a diagnostic fast. The diagnosis of hyperinsulinism is based on evidence of increased insulin secretion/actions at the time of hypoglycemia, including: a detectable insulin level, suppressed plasma betahydroxybutyrate (ketones), suppressed plasma free fatty acids, and a glycaemic response to glucagon. Diagnosis should be made in consultation with an endocrinologist familiar with hyperinsulinism.

Neonates with suspected BWSp should be screened for hypoglycaemia (**R40, 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)[131]. Management of HI includes medical therapies such as diazoxide, and somatostatin analogs (octreotide, lanreotide). Surgery (pancreatectomy) may be indicated if persistent hypoglycaemia occurs despite maximal medical therapies[132]. New therapies such as mTOR inhibitors (sirolimus) or GLP-1 receptor antagonists have been used in hyperinsulinism and very recently in BWSp [133] but, to date, no specific management (medical or surgical) has been evaluated in the context of BWSp (**R42**)

Two genes implicated in congenital hyperinsulinism, *ABCC8* and *KCNJ11,* map to chromosome 11p and rare patients with BWSp may carry a heterozygous mutation in either gene. If the genes are included in the isodisomy, then homozygosity for the mutation in disomic cells produces severe hypoglycaemia.[24] In cases of hypoglycaemia with hyperinsulinism without other traits suggestive of BWSp, investigations for 11p15.5 methylation abnormalities may be considered.

3.6 Management of Cardiac lesions (R44-R47)

Congenital heart disease is more prevalent in BWS than in the general paediatric population and cardiac defects may occur in up to 13-20% of patients [13,116,134] (**R44**). Minor anatomical defects (e.g. cardiomegaly, patent *ductus arteriosus* or *foramen ovale,* interatrial or interventricular defects) require echocardiographic monitoring until spontaneous resolution (usually) occurs (**R45**). More

severe defects may require surgical correction though the management will be similar to that in sporadic cases (**R47**).

Congenital long QT syndrome has been reported in two BWS families harbouring an intragenic deletion and a translocation at IC2 inactivating the *KCNQ1* gene, which, although very rare, is associated with a risk of sudden death (R46).[78,100]

3.7 Management of Neurological Features (R48-50)

Cognitive development is usually normal in BWSp, though developmental delay can be associated with prematurity, severe hypoglycaemia, unbalanced chromosome rearrangements or paternal genomewide upd[135] (**R48**). The differential diagnosis should be carefully considered in patients with presumptive BWS and learning disability but no 11p15 anomaly as some overgrowth disorders (e.g. Sotos, Malan and Simpson-Golabi-Behmel syndromes) are more frequently associated with developmental delay (see supplementary Table 2) (**R49**).

Recently, malformations of the central nervous system (e.g. abnormal posterior fossae/Dandy Walker malformations or abnormal corpus callosum or septum pellucidum) have been reported in rare patients (chiefly with a defect involving IC2)[76,136] and these may need to be considered in children with neurological symptoms or signs (**R50**).

3.8 Management of Renal Complications (R51-R55)

The prevalence of nephro-urological anomalies in BWSp is 28–61%.[137] A variety of anomalies have been described; cortical and medullary cysts occur in ~10% of patients and the prevalence of hypercalciuria and nephrolithiasis is increased.[138] Not all anomalies detected by ultrasonography will be of clinical significance but a minority of anomalies may be severe (and usually detectable prenatally) requiring medical or surgical management. Severe vesicoureteral reflux may cause kidney damage and recurrent urinary tract infections. Nephromegaly may be a marker of increased risk of Wilms tumour.[137]

Renal anomalies may occur in all molecular subtypes of BWSp but only certain groups may 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. Therefore, we recommend a nephrourological evaluation at clinical diagnosis and

at the time of transition for any patients with BWSp, and screening for nephrocalcinosis/stones only for patients who undergo abdominal USS for tumour screening (**R51-55**).

3.9 BWSp and Embryonal Tumours (R56-R67)

Embryonal tumours occur in ~8% of children with BWSp.[139] The most common types are Wilms tumour (WT, 52%), hepatoblastoma (HB, 14%), neuroblastoma (10%), rhabdomyosarcoma (5%) and adrenal carcinoma (3%).[17] Although there are some differences in mean age at diagnosis between tumour types, the overall cancer risk is highest in the first two years and then declines progressively approaching general population risk before puberty. 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: segmental upd(11)pat and GOM at IC1 have a higher risk than *CDKN1C* mutations and IC2 LOM.[49] The four main molecular subgroups are characterised by a cancer risk gradient: IC1 GOM (28%) > segmental upd(11)pat (16%) > *CDKN1C* mutation (6.9%) > IC2 LOM (2.6%).[17] In addition, there are also differences in the tumour types observed. Patients with IC1 GOM are mostly predisposed to develop WT (observed in 24% of cases and accounting for 95% of malignancies in this group). Conversely, patients with IC2 LOM and *CDKN1C* mutations usually do not develop WT but other tumours such as HB, rhabdomyosarcoma and neuroblastoma. Thus Maas et al (2016) found a prevalence of WT of ~0.2% (2/995) in patients BWSp and IC2 LOM and although a recent report suggested that the WT risk with IC2 LOM might be underestimated, only a single patient with WT was observed (Brzezinski et al 2017) so that the overall prevalence of WT with IC2 LOM is probably much less than 1%, Neuroblastoma is most strongly associated with *CDKN1C* mutations.[139] Patients with segmental upd(11)pat are predisposed to develop any of the tumour types seen in BWSp (see Table 3). Genomewide paternal upd appears to have a high risk of tumour development with types similar those in segmental upd(11)pat but with an increased incidence of hepatic/adrenal tumours and extending into adolescence/young adulthood.[135,140–142]

Specific studies are lacking on the tumour risk in patients with isolated LO and clinically diagnosed BWS with negative molecular testing. It appears plausible that the cancer risk in isolated LO cases that fall within the BWSp is linked to the type of 11p15.5 molecular anomaly. The tumour risk in ILO with segmental upd(11)pat is estimated to be as high as 32-50%.[119,143]

Tumour Surveillance Strategies

Tumour screening in inherited cancer predisposition syndromes aims to improve patient survival and reduce morbidity by earlier detection of tumours. However, no surveillance protocol can detect every tumour and there are both benefits and drawbacks to screening – the latter includes 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 and it may vary according to regional medical and medicolegal practices and local healthcare systems. Whereas screening is considered for a risk >1% in the USA, in Europe 5% may be considered an appropriate threshold.[8,144] Various protocols have been suggested for tumour surveillance in BWSp, usually comprising abdominal USS ± measurement of alpha fetoprotein (αFP) levels at various ages and intervals in infancy. Traditionally most protocols have been applied to all cases but the definition of specific epigenotype-tumour risk correlations provides a basis for more targeted surveillance protocols.

Screening for WT: Abdominal USS is the preferred modality for WT screening. The doubling time of WT cells, has been estimated to be 11–13 days[145] and USS is recommended every 3–4 months.[146,147] Given the high survival rate of WT (90% overall survival at 4 years), early detection of WT by surveillance is predicted to only marginally impact survival but diagnosis at an earlier stage may reduce the burden of treatment-related morbidity[148–151].

If WT screening is targeted by molecular subgroup then IC1 GOM and segmental upd(11)pat cases are at highest risk and several groups have suggested that IC2 LOM cases should not be offered USS in order to avoid excessive medicalization and possible false-positive results.[139,144]

Screening for Hepatoblastoma: the risk of HB in BWS is >2000-fold higher than in the general population and HB is the second most common tumour type in BWS[15]. However specific studies on HB screening in BWS are lacking. Abdominal USS is a first line investigation in a child with a suspected liver mass although not all parts of the liver may be imaged easily and small tumours may be missed[152]. Concerns about the sensitivity of abdominal USS led to suggestions that it should be combined with serum αFP measurements which is secreted by >95% of HB.[153–155] Treatment and outcome of patients with HB is closely connected to tumour stage at diagnosis and preliminary data suggested that αFP screened BWSp cases with HB have a lower stage and a better prognosis than unscreened cases and that increased serum αFP may precede HB detection by USS.[156] However, this is unproven and further data is required. In the paediatric setting interpreting serum αFP levels can be complex, with a wide range and variable concentrations in early infancy. [157,158] Serum αFP levels may be higher in BWS babies without HB than in normal age-matched controls . In view of the burden of repeated venepuncture and the complexity of interpreting raised αFP levels it has been debated whether benefits of αFP screening in BWSp outweigh the drawbacks[159–162] and the

consensus voted not to recommend αFP screening (**R64**).

Screening for neuroblastoma: although reported in all molecular subgroups, neuroblastomas are preferentially associated with *CDKN1C* mutations with a frequency of ~4% (see Table 3). Detection of asymptomatic neuroblastomas by determination of the urinary tumour markers vanillylmandelic and homovanillic acid and/or catecholamines to creatinine ratio, combined with three monthly USS until 2-3 years of age has been suggested.[139] However, previously neuroblastoma screening by urinary markers in large scale paediatric setting had very low impact on the related morbidity and mortality rates [163,164] and currently there is no evidence that neuroblastoma screening in BWSp would improve treatment and survival (**R65**).

Surveillance for other tumour types: screening for adrenal carcinoma has been suggested in BWSp with the help of clinical evaluation, adrenal USS and determination of serum dehydroepiandrosterone sulphate (DHEAS) every 4-6 months. However, adrenal carcinoma is rare in BWS (even in those with segmental upd(11)pat and genome-wide paternal upd who are at highest risk) and there is no data on the utility of such screening in BWSp (those with segmental upd(11)pat and genome-wide paternal upd are at highest risk).

BWSp/ILO Consensus Tumour Surveillance Protocol

The Consensus agreed that surveillance should be targeted to those molecular subgroups of BWSp that were at highest risk and that children with BWSp and IC2 LOM should not be offered routine USS (**R60**) (though there should be a low threshold for investigation in response to symptoms or parental concern). Other BWSp molecular subgroups and those with classical BWS and no detectable molecular anomaly should be offered 3 monthly abdominal USS until age 7 years (**R57-59, R61-63)** (see Table 3). It was agreed that αFP measurements should not be offered routinely because the incidence of HB was judged too low to deserve specific screening, the impact of surveillance of patients and families is unclear and the difficulties in interpretation may may lead to false positive results (**R64**). Nevertheless, in specific health care systems, clinicians may 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 low risk children with BWSp to be spared 3 monthly USSs and, though for example the risk of WT is small in *CDKN1C* mutation cases, applying a common surveillance modality (i.e. abdominal USS rather than renal USS in some groups, liver on other subgroups etc.) 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% threshold risk for surveillance and so recommended abdominal USS and αFP screening for all cases of BWSp[165]. Both groups made their 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 been already been adopted in some countries[17,144]. Hence the difference in screening recommendations between the two groups reflects mainly the different medical and medicolegal cultures in North America and Europe. Whilst a universally agreed screening protocol would usually be preferable, taking into account the different conclusions between the AACR group and this consensus experts' group, 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[165].

Management of BWSp-related tumours

Children with BWSp and WT, when compared to non-syndromic cases, present with lower-stage disease, less metastatic disease, fewer anaplastic tumours and a higher incidence of bilateral synchronous or metachronous recurrence[150] (**R67**). The latter seem to be connected to the presence of multifocal or diffuse nephrogenic rests in one or both kidneys (nephroblastomatosis)[166], a feature not easily distinguishable from WT on standard imaging.[149] BWSp patients with WT diagnosed though abdominal USS surveillance have a smaller tumour size than children with sporadic WT [146] but survival rates are similar (at least 90% at 4 years)[150]. Smaller WT are more amenable to partial nephrectomy and nephron sparing strategies (i.e. partial nephrectomy) are particularly preferred in BWSp patients given the potential co-occurrence of progressive non-malignant renal diseases and bilateral WT.[147] Recent data show comparable outcomes after nephron sparing surgery or total nephrectomy in BWSp WT patients with only 9% of recurrence or metachronous disease and 4% of deaths.[149]

3.10 Late onset complications (R68-R70)

Features of BWSp such as macroglossia and postnatal overgrowth tend to ameliorate with age and so 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.

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 (see Supplementary Table 3) there is no evidence of a specific tumour risk that might justify surveillance. However, follow-up of large series of BWS adults have not been published. Children with BWSp treated for embryonal tumours may develop late-onset complications from surgery, radiotherapy or chemotherapy similar to children with sporadic tumours.

Cardiovascular: patients with congenital heart disease require appropriate follow up in adult specialty clinics. Rarely cardiovascular defects may be diagnosed in adulthood for the first time[167] but routine screening is not indicated. Rare patients with IC2 CNVs/rearrangements that may predispose to long-QT syndrome will require follow up throughout adulthood.

Infertility: congenital anomalies of the urogenital tract (e.g. bicornuate uterus) have been described[167,168] but there is no clear evidence of excess fertility problems in women with BWSp. Reduced fecundity has been described in affected males (compared to females)[169] but the frequency of infertility in men with BWSp is unknown.

Renal: although examples of the diagnosis of renal anomalies in adults with BWSp have been reported [168] it is assumed that, if renal USS was performed, renal abnormalities would usually be detected in childhood.

Although regular surveillance (e.g. echocardiography, renal function testing, evaluation of hearing) has been suggested for adults with BWSp[167], 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 agreed that a detailed clinical review and renal USS (see Supplementary Table 4) should be undertaken at age 16 years and specific recommendations for continued surveillance based only on ongoing problems (**R68**). Adults with BWSp should be encouraged to seek genetic counselling advice before starting a family (**R69**). At that stage any potential concerns about fertility can be reviewed and referrals for further investigation made as appropriate.

3.11 Psychological and counselling aspects

The diagnosis of a disorder such as BWSp can have wide-ranging impacts on the psychological and social wellbeing of families. Though the precise effects will vary between families and be influenced by individual medical and social details and each family may face different challenges, it is

important that all health professionals be aware of the wider non-medical issues that may be relevant to the family (**R71**). There is relatively little information on psychosocial aspects that might be specific to BWSp. 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 apparently differing medical practices and recommendations may cause parental uncertainty and anxiety. A survey of parents of BWSp children with macroglossia revealed widespread parental concerns about the "negative cosmetic appearances" of a large protruding tongue and persistent drooling which to led to strangers staring and questioning whether their children had learning difficulties.[125] Parents are also concerned that this may 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.[170] Health care professionals should be aware that psychosocial difficulties may occur and be prepared to refer families to specialists such as genetic counsellors, social workers and psychologists as appropriate. Support groups can play a key role in helping families adjust to the diagnosis, share their concerns and experiences and obtain the correct care and support and all families should be given the contact details of relevant groups (**R72**).

Conclusions

The recommendations of the first international BWS consensus group provide a framework for improving the diagnosis and management of BWSp. BWSp is characterised by complex genetics and variable multisystem phenotypes and it is important that a lead clinician is identified for each patient (**R22**) to ensure coordination of the numerous aspects of care throughout childhood (see Supplementary Table 4). The proposed diagnostic and care pathways are intended to be practical and cost effective (e.g. targeting tumour surveillance to high risk groups should reduce costs compared to universal surveillance). Nevertheless in some health care systems and medicolegal environments further evidence may be required to shift clinical practice (e.g. tumour surveillance in North America). Therefore it is important that implementation of the consensus recommendations should be accompanied by prospective audits in order to expand the evidence base for future consensus initiatives.

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Text Boxes

Text Box 1: Details of Consensus Voting Process

For voting on individual recommendations participants 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

Text Box 2: Consensus recommendations for Clinical Working Group (see relevant section for background information)		
Beckwith-Wiedemann Spectrum Scoring System and Clinical indications for molecular testing of BWS		
1	Beckwith-Wiedemann spectrum (BWSp) is usually caused by dysregulation of the 11p15 imprinted region and involves overgrowth in multiple tissues often in a mosaic state. BWSp encompasses a range of phenotypes and children may 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 (Figure 1). A third subset is defined as patients with an 11p15 anomaly who do not fit into these first two groups. **A+++**	**Section 1.2**
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, which are summarized in Table 1: a score of 4 or more 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 (LO) is defined as significant 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 LO 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 testing anyone suspected of being in the BWSp (LO, classical BWS, or features in Table 1). For simplicity, we would recommend testing for any patient with 2 or more points from Table 1. In cases where isolated omphalocele/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	Hyperinsulinism: Hypoglycemia is defined as plasma glucose levels below 50 mg/dL for the first 6 hours of life and below 60 mg/dL thereafter. Hyperinsulinism is defined as a glucose infusion rate of greater than or equal 8 mg/kg/min, a detectable insulin level and/or C-peptide, undetectable 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++**	**Section 1.2**
BWS and Assisted Reproduction Technology (ART)		
6	There is an established association between ART and BWS. The absolute risk of BWS in an ART conception is estimated to be very low (no more than 1:1000). Additional research is needed to further characterize this association and the relationship between subfertility, hormonal stimulation, embryo manipulation and imprinting defects. **A+++**	**Section 1.3**

Text Box 3: Consensus recommendations for Molecular Working Group (for background information see relevant section)		
Molecular genetic analysis		
7	Molecular genetic testing should be performed by a health professional experienced in the field of imprinting disorders. Recommended nomenclature should be adopted in publications and in test reporting. **A+++**	Section 2
8	The flow-chart outlined in Fig. 3 should be followed for molecular diagnosis of BWSp. **A+++**	Section 2.1
9	First-line molecular testing should include DNA methylation analysis of the H19/IGF2:IG-DMR (IC1) and KCNQ1OT1:TSS-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+++**	Section 2.1
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+++**	Section 2.2
11	Detailed analysis of the H19/IGF2:IG-DMR should be considered in individuals with GOM of this region, since SNVs / small CNVs can occur in these cases and confer high risk of recurrence [prioritized in the presence of a positive family history]. **A+++**	Section 2.2
12	In case of a negative methylation test result, second-line molecular testing should be considered, and may include: sequencing of the coding exons and the exon–intron boundaries of *CDKN1C* [prioritized in the presence of a positive family history, cleft palate, or abdominal wall defect (umbilical hernia or exomphalos)] **A+++**	Section 2.3
13	In case of a negative methylation test result, second-line molecular testing	Section

	should be considered, and may include: analysis of additional tissues to detect somatic mosaicism (prioritized in the presence of asymmetric overgrowth). **A+++**	2.3
14	In case of a negative methylation test result, second line molecular testing should be considered and may include: further tests for rare chromosomal rearrangements **A+++**	Section 2.3
15	In case of a negative methylation test result, second-line molecular testing should be considered, and may include: re-evaluation of the clinical diagnosis and reconsideration of differential diagnoses. **A+++**	Section 2.3
16	Genetic counselling should be performed by a health professional experienced in the field of imprinting disorders. **A+++**	Section 2.5
17	Since the recurrence risk associated with genetic defects (e.g. *CDKN1C* loss of function variants, CNVs and DMR SNVs) is dependent on their size, location and parental origin, this should be taken into consideration during counselling for the family. **A+++**	Section 2.5
Prenatal molecular genetic analysis		
18	Prenatal molecular diagnostic investigations should be considered if a) prenatal ultrasonography reveals potential features of BWSp and reaching a specific diagnosis (or excluding other potential conditions) or b) positive family history with a known molecular defect is present, which would influence the management of the relevant pregnancy. **A+++**	Section 2.6
19	The flow-chart indicated for post-natal testing is not necessarily applicable to prenatal testing. Modification depends on the individual setting (e.g. known molecular defects, specific clinical features). **A+++**	Section 2.6
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	Section 2.6

	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 is contributed to multicentre audits to enable best practice guidelines to be further developed and refined. **A+++**	Section 2.6

Text Box 4: Recommendations from Management Working Group		
22	It is recommended that each patient with BWSp should have an experienced lead health care provider who will organise the referral to each specialist, and will coordinate care for the patient. A+++	
Prenatal management		
23	If a diagnosis of BWSp is suspected or confirmed in the prenatal period, then potential BWSp-related foetal and maternal complications (e.g. foetal congenital anomalies, shoulder dystocia from macrosomia, postnatal hypoglycaemia and maternal preeclampsia) should be anticipated and appropriate clinical care should be performed. A+++	Section 3.1
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+++	Section 3.1
Growth and lateralised overgrowth		
25	Growth charts from BWSp patients are needed. A+++	Section 3.2
26	Physicians should be aware of the rare possibility of final height above +2SDs. Postnatal growth and pubertal development should be monitored at least annually until the end of growth. A++	Section 3.2

27	Appropriate interventions may be proposed in case of possible tall stature with the same procedures as for other patients with tall stature. A++	Section 3.2
28	Monitoring of leg length discrepancy should be based on clinical examination. A++	Section 3.2 (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+++	Section 3.2 (LO)
30	Shoe-lifts may be indicated for LLD less than 2 cm. Epiphysiodesis is usually indicated for predicted LLD above 2 cm. Reversible epiphysiodesis may be preferred. A++	Section 3.2 (LO)
31	Lengthening of the shorter normal limb should be considered only for specific cases. A+++	Section 3.2 (LO)
32	Surgical correction of upper limbs asymmetric overgrowth is generally not indicated. A+++	Section 3.2 (LO)
Management of macroglossia		
33	If significant airway obstruction is suspected, a careful evaluation including sleep studies/pulmonologist consultation and ENT consultation should be performed. A+++	Section 3.3

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+++	Section 3.3
35	Surgical intervention (adenoid tonsillectomy +/- tongue reduction surgery) should be considered earlier in case of severe airway obstruction. A+++	Section 3.3
36	In case of feeding difficulties, support from a feeding specialist and dietetics should be proposed. A+++	Section 3.3
37	Tongue reduction surgery should be performed by an experienced surgical team after detailed assessment by a multidisciplinary team (including pediatric anaesthesiologist, intensive care unit, surgeon, speech therapist, orthodontist) preferably in a reference centre. A+++	Section 3.3
38	The results of surgery should be carefully audited and postoperative follow-up should continue until age 16 years. A+++	Section 3.3
Management of Exomphalos		
39	Treatment of exomphalos in the context of BWSp should be in accordance with general recommendations for the treatment of exomphalos though in BWSp-associated cases attention should be paid to the risk of hypoglycaemia and the anaesthetic risk from macroglossia. A+++	Section 3.4
Management of Hypoglycaemia		

40	Capillary blood glucose should be monitored in neonates with a clinical suspicion or confirmed diagnosis of BWSp for 48 hours. Hypoglycaemia should be defined by two consecutive (30 minutes) glucose levels lower than 50 mg/dl 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++	Section 3.5
41	A diagnostic fasting test (including measurement of glucose, insulin, ketones after 6 hours of fasting for full-term babies and 4 hours for preterm babies) should be done for neonates with a suspicion of BWSp before discharge from the nursery 48 hours after birth. A++	Section 3.5
42	No specific management of hyperinsulinism/hypoglycaemia has been proposed in the context of BWSp and management of hyperinsulinism/hypoglycaemia should be performed according to general recommendations. A++	Section 3.5
43	In case of severe persistent hyperinsulinism in a BWSp patient, additional causes of hyperinsulinism should be looked for. A+++	Section 3.5
Management of cardiac lesions		
44	Physicians should be aware of the increased frequency of cardiac anomalies in BWS children with BWSp. A++	Section 3.6
45	A baseline clinical cardiovascular examination should be performed at diagnosis in all children with clinical/molecular diagnosis of patients with BWSp. Individuals with clinically detected or suspected cardiovascular abnormalities should be referred for specialist cardiac assessment and echocardiography. A+++	Section 3.6

46	Annual evaluation and electrocardiogram are recommended in patients with genomic rearrangements involving the IC2 (KCNQ1OT1:TSS-DMR) region. B+	Section 3.6
47	Management and follow up of congenital cardiac lesions (e.g. VSD etc.) should be as in the non-BWSp population. A+++	Section 3.6
Management of Neurological Features		
48	Cognitive development should be monitored by the paediatrician. Particular attention should be paid to those with risk factors such as preterm birth, neonatal hypoglycemia, and carriers of chromosome rearrangements or paternal genomewide UPD. A+++	Section 3.7
49	For patients with a clinical diagnosis of BWSp and learning disability and no molecular or chromosomal anomaly, other potential diagnoses should be considered and excluded (Supplementary Table 2)A+++	Section 3.7
50	Neurological investigations including MRI may be indicated only in children with neurological symptoms. A++	Section 3.7
Management of Renal Complications		
51	At diagnosis of BWSp all patients should be screened for nephrourological malformations by clinical evaluation and ultrasound. A+++	Section 3.8
52	Physicians should be aware of the possibility of hypercalciuria, which can lead to nephrocalcinosis. A++	Section 3.8

53	Patients with US-detected anomalies should be referred to a paediatric nephrologist/urologist for specific follow-up. A+++	Section 3.8
54	For patients undergoing abdominal surveillance for tumour screening, physicians and radiologists should pay attention to the possibility of nephrocalcinosis and/or stones. A+++	Section 3.8
55	For patients with BWSp, at the time of adult transition, a nephrourological evaluation (clinical examination, blood pressure and ultrasound) should be performed. A++	Section 3.8
BWSp and Embryonal Tumours		
56	Screening should be stratified according to the genotype. A+++	Section 3.9
57	Abdominal ultrasound for BWSp-related tumours each 3 months until the 7th birthday is recommended for all patients with BWSp other than patients with isolated IC2 LOM. A++	Section 3.9
58	For patients with BWSp and upd(11)pat, abdominal ultrasound for WT and hepatoblastoma each 3 months until 7 years is recommended. A+++	Section 3.9
59	For patients with BWSp and IC1 GOM (H19/IGF2:IG DMR), abdominal ultrasound for WT each 3 months until 7 years is recommended. A+++	Section 3.9

60	For patients with BWSp and IC2 LOM (KCNQ1OT1:TSS DMR), no tumour surveillance is recommended. AB+	Section 3.9
61	For patients with BWSp and CDKN1C mutation, abdominal ultrasound for neuroblastoma each 3 months until 7 years is recommended. A+	Section 3.9
62	For patients with BWSp and 11p15 duplication, abdominal ultrasound for WT each 3 months until 7 years is recommended. A+++	Section 3.9
63	For patients with classical BWS without molecular defect, abdominal ultrasound each 3 months until 7 years is recommended. A++	Section 3.9
64	αFP screening is not recommended for patients with BWSp A+	Section 3.9
65	Catecholamines screening is not recommended for patients with BWSp A+++	Section 3.9
66	There should be a lower threshold for investigation in case of possible tumour-related symptoms or in response to parental concerns. A+++	Section 3.9

67	Treatment of tumours in patients with BWSp may 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+++	Section 3.9
Late onset complications		
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 health services. A+++	Section 3.10
69	Young adults with BWSp should be alerted to the availability of genetic counselling so that they can seek advice prior to them starting a family. A+++	Section 3.10
70	Given the paucity of data on the long-term health effects of a diagnosis of BWSp, further research should be undertaken. A+++	Section 3.10
Psychological and counselling aspects		
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 for children and family if required. A+++	Section 3.11

72	When the clinical diagnosis is confirmed, parents should be offered the contact details of BWSp support groups. A+++	Section 3.11

Tables

Table 1. Clinical Features of Beckwith-Wiedemann Spectrum (BWSp)

Cardinal Features (2 points per feature)	**Suggestive Features (1 point per feature)**
Macroglossia	Birth Weight >+2SD
Exomphalos	Facial naevus simplex
Lateralised overgrowth	Polyhydramnios/Placentomegaly
Multifocal/bilateral Wilms tumour or Nephroblastomatosis	Ear creases/pits
Hyperinsulinism (see text)	Transient hypoglycaemia/hyperinsulinism (see text)
Pathology findings: Adrenal cortex cytomegaly Placental mesenchymal dysplasia Pancreatic adenomatosis	Typical BWSp tumours (neuroblastoma, rhabdomyosarcoma, unilateral WT, hepatoblastoma, adrenocortical carcinoma, phaeochromocytoma)
	Nephromegaly/Hepatomegaly
	Umbilical hernia/Diastasis recti

Table 2: Summary of BWSp molecular defect categories and recurrence risk.

Molecular defect	Frequency	Mosaicism observed	Recurrence risk	Characteristic clinical features (compared to other molecular subgroups)
IC1 GOM	5%	+	If no genetic anomaly present – <1% If genetic anomaly (e.g. pathogenic single nucleotide variant of copy number variant in DMR) present – 50%, dependent on parental origin	Lower frequency of exomphalos Higher risk of Wilms tumour
IC2 LOM	50%	+	If no genetic anomaly identified – <1% If *cis*-acting genetic anomaly present – 50%, dependent on parental origin	Higher frequency of exomphalos Low risk of Wilms tumour
upd(11)pat	20% (see also paternal uniploidy)	+	<1%	Higher incidence of lateralised overgrowth Lower frequency of exomphalos Higher risk of Wilms tumour and hepatoblastoma
Loss-of-function *CDKN1C* variants	5% (40% in familial cases)	±	50% on maternal transmission	Higher frequency of exomphalos Low risk of Wilms tumour
Dup(11)(p15.5)pat	~2%	-	50% on paternal transmission; Risk for SRS on maternal transmission	

Deletions involving 11p15	<1%	-	Dependent on extent and position of CNV, and parent of origin	
mosaic paternal unidiploidy (Genomewide patUPD)	Up to 10% of upd(11)pat	+	Low	Higher frequency of neoplasia;
MLID	33% of IC2 LOM cases	+	Low unless *in trans* genetic variant identified	Unclear

Table 3. Proposed tumour surveillance protocol for patients with Beckwith-Wiedemann spectrum disorder (BWSp including those with ILO with 11p15 abnormalities) differentiated according molecular subtype. Though 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 health care systems practice may currently vary from this protocol (see text).

Tumour risks in individual molecular groups	**Primary Target Tumour Type for Surveillance**	**Surveillance procedures**	**Timing**
IC2-LOM overall risk tumour =2.6%			
Hepatoblastoma (0.7%) Rhabdomyosarcoma (0.5%) Neuroblastoma (0.5%) Thyroid cancer (0.3%) WT (0.2%) Melanoma (0.1%)	Tumour incidence very low, extremely variable tumour spectrum, only half of tumours arising into abdomen	No routine ultrasound (USS) surveillance. Clinical assessment and USS in response to signs/symptoms or parental concerns	
IC1-GOM overall tumour risk =28.1%			
Wilms tumour (24.0%) Neuroblastoma (0.7%) Pancreatoblastoma (0.7%)	Wilms tumour	Abdominal USS	3 monthly from diagnosis to 7 years of age
upd(11)pat overall tumour risk =16%			

Wilms tumour (7.9%) Hepatoblastoma (3.5%) Neuroblastoma (1.4%) Adrenocortical carcinoma (1.1%) Phaeochromocytoma (0.8%) Lymphoblastic leukaemia (0.5%) Pancreatoblastoma (0.3%) Haemangiotheloma 0.3%) Rhabdomyosarcoma 0.3%)	Wilms tumour Hepatoblastoma Adrenal tumours	Abdominal USS	3 monthly from diagnosis to 7 years of age Note that 7 years refers to the risk of WT, as HB usually occurs before the age of 2
CDKN1C mutation– overall tumour risk =6.9%			
Wilms tumour (1.4%) Neuroblastoma (4.2%)) Acute lymphatic leukaemia (1.4%)	Neuroblastoma	Abdominal USS	3 monthly from diagnosis to 7 years of age
Classical BWS with negative molecular tests – estimated overall tumour risk =6.2%			
Wilms tumour (4.1%) Neuroblastoma (0.6%) HB (0.3%) Rhabdomyosarcoma (0.3%) Adrenocortical carcinoma (0.3%)	Wilms tumour	Abdominal USS	3 monthly from diagnosis to 7 years of age

* Tumour and histotype prevalence from Maas *et al*.[17] and Mussa *et al.*[116]

Figure Legends

Figure 1: Beckwith-Wiedemann Spectrum. The Beckwith-Wiedemann Spectrum (BWSp) includes patients with a clinical diagnosis of 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 (ILO) and an (epi)genetic change at the BWS locus. The dotted arrowed line to the left indicates that some patients with apparent ILO and no 11p15 abnormality may 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 may be further investigated as in Figure 3.

Figure 2. The BWS locus at chromosome 11p15.5. Only the imprinted genes that within the centromeric and telomeric domains implicated in the pathophysiology of the Beckwith-Wiedemann syndrome are represented. Genes expressed from the maternal chromosome are depicted as red boxes, those expressed from the paternal allele as blue boxes. Grey boxes indicate non-expressed alleles. Filled lollipops indicate methylated ICs, open lollipops unmethylated ICs. Bent arrows indicate transcription orientation. Mat, maternal chromosome; pat, paternal chromosome.

Figure 3. Flow chart for investigation and diagnosis of BWS. Clinical questions are in blue boxes, recommended molecular tests in yellow boxes, molecular diagnosis in pink boxes, molecular testing to be considered in green boxes. CMA, chromosome microarray analysis, which can be oligonucleotide- and/or SNP-based platforms.

Key:
CNV, copy number variation. SNV, Single nucleotide variation. SNP, Single nucleotide polymorphism. LoM, Loss of methylation. GoM, gain of methylation.
[1]ICNV status may be determined simultaneously with methylation testing
[2]refer to text for indications for testing [3]del(11)(p15.5)mat may be detected with lower frequency

Figure 1:

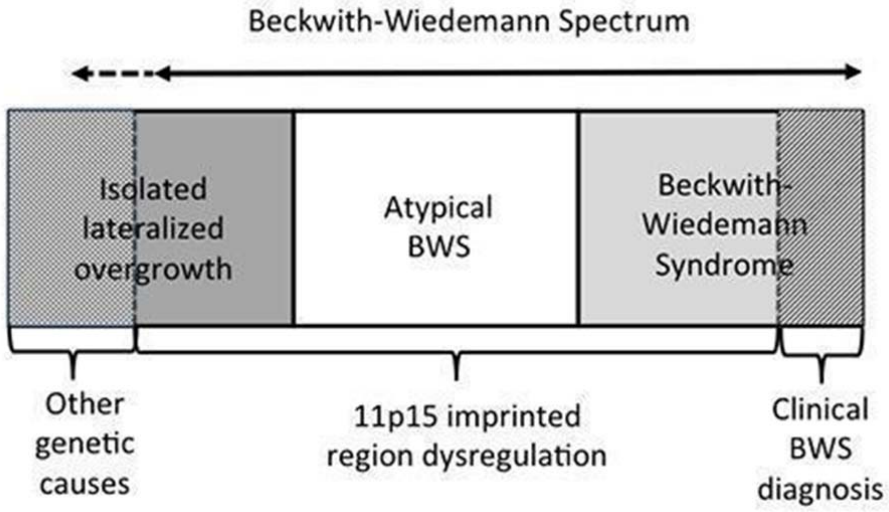

Beckwith-Wiedemann Spectrum
Isolated lateralized overgrowth
Atypical BWS
Beckwith-Wiedemann Syndrome
Other genetic causes
11p15 imprinted region dysregulation
Clinical BWS diagnosis

Figure 2

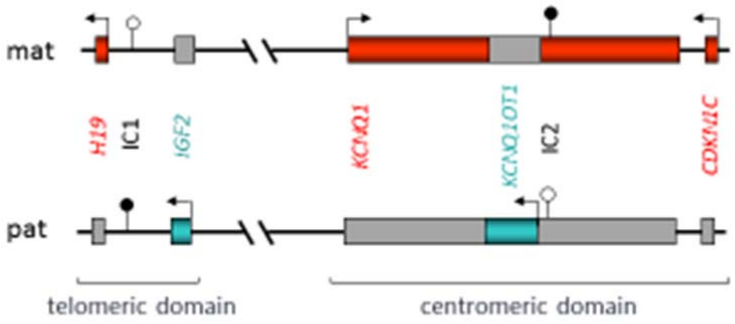
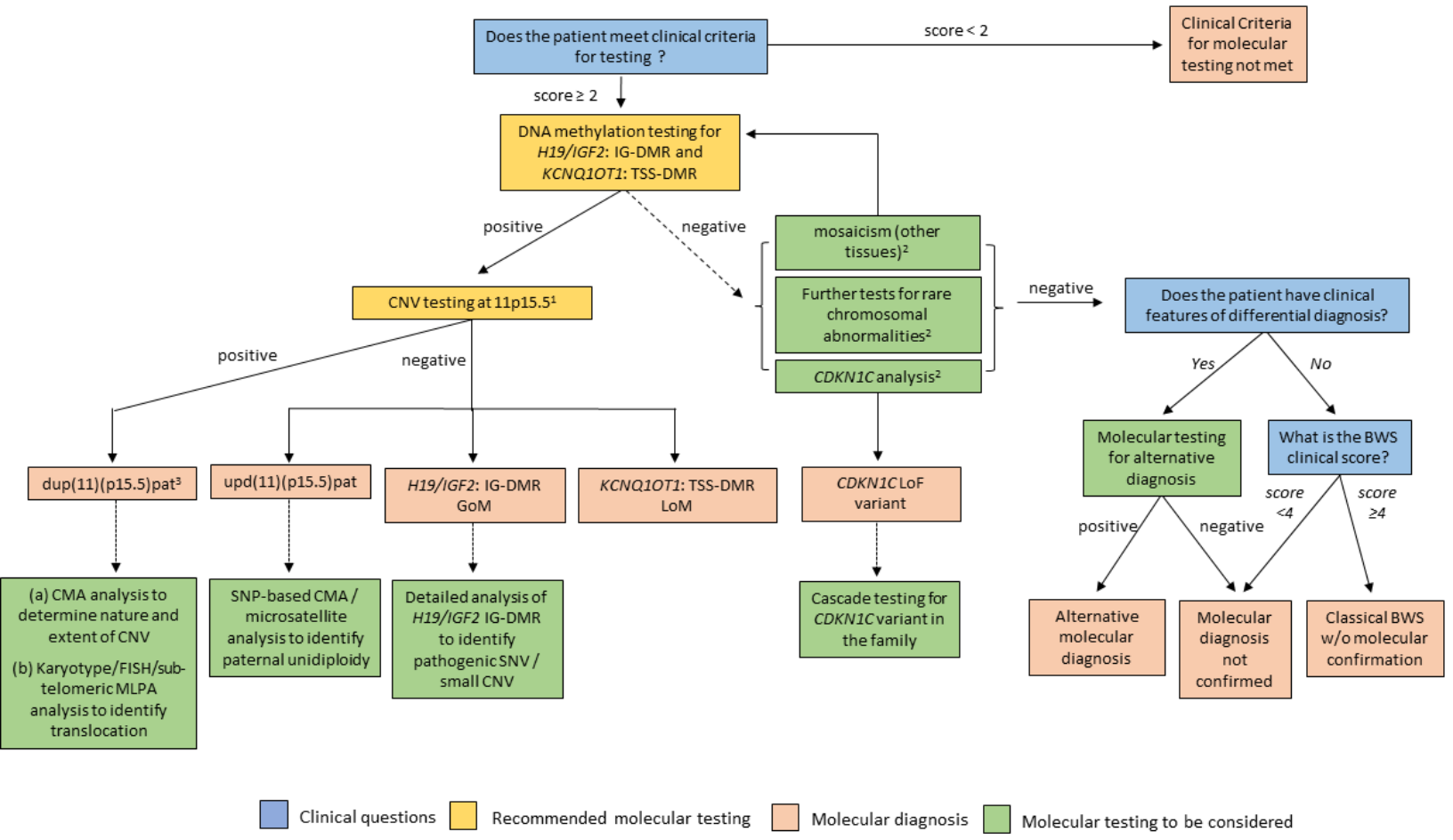

mat
H19
IC1
IGF2
KCNQ1
KCNQ1OT1
IC2
CDKN1C
pat
telomeric domain
centromeric domain

Figure 3


Does the patient meet clinical criteria for testing ?
score < 2
Clinical Criteria for molecular testing not met
score ≥ 2
DNA methylation testing for H19/IGF2: IG-DMR and KCNQ1OT1: TSS-DMR
positive
negative
CNV testing at 11p15.5[1]
mosaicism (other tissues)[2]
Further tests for rare chromosomal abnormalities[2]
CDKN1C analysis[2]
negative
Does the patient have clinical features of differential diagnosis?
Yes
No
positive
negative
dup(11)(p15.5)pat[3]
upd(11)(p15.5)pat
H19/IGF2: IG-DMR GoM
KCNQ1OT1: TSS-DMR LoM
CDKN1C LoF variant
Molecular testing for alternative diagnosis
What is the BWS clinical score?
positive
negative
score <4
score ≥4
(a) CMA analysis to determine nature and extent of CNV
(b) Karyotype/FISH/sub-telomeric MLPA analysis to identify translocation
SNP-based CMA / microsatellite analysis to identify paternal unidiploidy
Detailed analysis of H19/IGF2 IG-DMR to identify pathogenic SNV / small CNV
Cascade testing for CDKN1C variant in the family
Alternative molecular diagnosis
Molecular diagnosis not confirmed
Classical BWS w/o molecular confirmation
Clinical questions
Recommended molecular testing
Molecular diagnosis
Molecular testing to be considered

Supplementary Information for

Clinical and Molecular Diagnosis, Screening and Management of Beckwith-Wiedemann syndrome: An International Consensus Statement

Contents:

Supplementary Table 1: Frequent clinical manifestations of BWSp from nine selected studies

Characteristic	Major	Minor	Estimated Prevalence in Spectrum [9,12,13,17-22]
Macroglossia	9,13-16,116		85%
Macrosomia (pre/post-natal overgrowth defined as >90th or >97th percentile)	9,13-16,116		67%
Abdominal wall defects General Exomphalos or umbilical hernia Exomphalos, diastasis recti or umbilical hernia Diastasis recti	13 9 16 14,116 15	 14,116	General - 68 % Exomphalos – 44% Umbilical hernia – 44% Diastasis recti – 22 %
Organomegaly Nephromegaly	9,14,116	 13	General – 53% Nephromegaly – 38% Hepatomegaly – 37% Splenomegaly – 16%
Lateralised overgrowth	14,116	9,13,16	37%
Neonatal hypoglycaemia	15	9,13,14,16,116	51%
Facial naevus flammeus (simplex)		9,13,14,16,116	52%
Ear creases/pits	14,15,116	9,13,16	63%
Characteristic facial features (including midface underdevelopment, infraorbital creases, prominent mandible)		14,16	
Cardiac anomalies		14,16,116	20 %
Pregnancy-related findings (polyhydramnios, prematurity, enlarged placenta, thickened umbilical cord, placental mesenchymal dysplasia)		14,16,116	Polyhydramnios – 53%
Embryonal tumour	14,116		
Renal abnormalities	14,116		52%
Positive family history	14,116		
Cleft palate	14,116		3 %
Advanced bone age		14,116	
Polydactyly		116	3 %
Supernumerary nipples		116	

Supplementary Table 2: Differential diagnosis of Beckwith-Wiedemann Spectrum

Disorder	Inheritance	Molecular findings	Clinical features	References
Simpson–Golabi–Behmel syndrome	X-linked recessive	Mutation in *GPC3*	Pre and postnatal overgrowth Macrocephaly Variable learning disability Umbilical hernia Diastasis recti Organomegaly Cardiac anomalies Diaphragmatic hernia Skeletal anomalies including postaxial polydactyly Supernumerary nipples Cleft palate Macroglossia Embryonal tumours (especially Wilms tumour) Coarse facial features	[171]
Perlman syndrome	Autosomal recessive	Homozygous mutations in *DIS3L2*	Prenatal overgrowth Developmental delay Hypotonia Nephromegaly Hyperinsulinism High risk Wilms tumour High neonatal mortality Facial features: prominent forehead, deep set eyes, broad flat nasal bridge, inverted V-shape upper lip	[172]
Costello syndrome	Autosomal dominant (frequent *de novo* mutations)	Activating mutation in *HRAS*	Polyhydramnios, often severe Increased birth weight due to oedema Macrocephaly Short stature Severe feeding difficulties and failure to thrive in infancy Mild to severe learning disability Cardiac anomalies, cardiomyopathy, arrhythmia Ulnar deviation Deep palmar and plantar creases	[173]

			Embryonal tumours (rhabdomyosarcoma and neuroblastoma) Coarse facial features Papillomata	
Sotos syndrome	Autosomal dominant (frequent *de novo* mutations)	Mutation in or deletion of *NSD1*	Tall stature Macrocephaly Mild to severe learning disability Scoliosis Seizures Cardiac anomalies Renal anomalies Neonatal hypotonia, jaundice and poor feeding Facial features: broad and prominent forehead, sparse frontotemporal hair, downslanting palpebral fissures, malar flushing, long and narrow chin	[174]
Weaver syndrome	Autosomal dominant (frequent *de novo* mutations)	Mutation in *EZH2*	Tall stature Macrocephaly Variable learning disability Camptodactyly Soft/doughy skin Umbilical hernia Facial features: broad forehead, hypertelorism, pointed chin, large ears and retrognathia in early childhood	[175]
Malan syndrome	Autosomal dominant	Mutation in the DNA-binding domain of *NFIX*	Postnatal overgrowth Rarely prenatal overgrowth Decrease of height overgrowth with age Persistent macrocephaly Invariably learning disability Frequent autism and anxiety Hypotonia Brain anomalies Slender body build Facial feature: long face, prominent forehead, short nose, long philtrum, prominent chin	[176]
PTEN hamartoma	Autosomal dominant	Mutation in *PTEN*	Prenatal overgrowth Macrocephaly	[177]

tumour syndrome			Hypotonia Learning disability Autism spectrum disorder Dermatological features including genital freckling, trichilemmomas, papillomatous papules, acral keratosis Lipomas Hamartomatous intestinal polyposis High risk of thyroid, breast, endometrial and other cancers	
PIK3CA related overgrowth spectrum	Somatic mosaic	Somatic activating mutation in *PIK3CA*	Segmental overgrowth syndromes including Fibroadipose hyperplasia, CLOVES syndrome, Hemihyperplasia multiple lipomatosis syndrome (HHML), Megalencephaly-capillary malformation (MCAP)	[178]

Supplementary Table 3: Adult onset tumours reported in BWSp

Tumour Type	Age at diagnosis (years)	Tumour studies	Molecular cause of BWS	Comment	Reference
ACTH secreting pituitary adenoma	19	Somatic mutation of *USP8* gene	IC2 epimutation		179
Recurrent virilising adrenocortical tumour Multiple breast fibroadenomas	16 (recurrence at 18) 19	Genome wide mosaic paternal uniparental disomy in both tumours	Mosaic genome wide UPD-pat		141
Ectopic adrenocortical virilising adenoma Pancreatic cancer*	20 24*	Genome wide upd Genome wide upd*	Genome wide upd	Previous history of Wilms tumour	180 *Tenorio and Lapunzina (personal communication).
Adrenal virilising adenoma	45	Loss of heterozygosity at HRAS (11p15.5)			168
Bilateral adrenal phaeochromocytoma	20	Not performed	Not recorded	Also history of bilateral breast adeno fibromas	181
Acute myeloid leukaemia	23	Not performed	Not recorded		182

Supplementary Table 4: Checklist for clinical management of patients with Beckwith-Wiedemann Spectrum

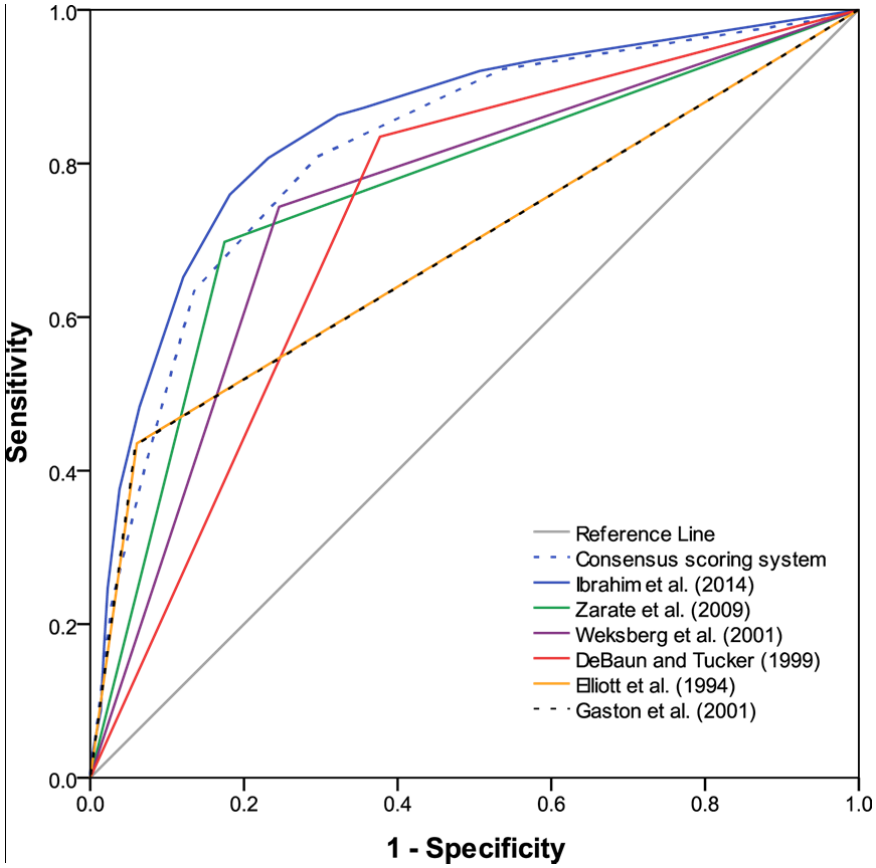
	At diagnosis		Management in childhood		At transition to adult care
	Diagnosis at birth	**Diagnosis in childhood**	**3 monthly age 3 months – 7 years (all except IC2 LOM)**	**Annually**	
Measure, record and monitor height, weight, and head circumference	R	R	-	R	R
Monitor leg length discrepancy and asymmetry	R	R	-	R	R
Assess for complications of macroglossia	R	R	-	R	R
Manage exomphalos appropriately if present	R	-	-	-	-
Screen for hypoglycaemia	R	-	-	-	-
Cardiovascular examination	R	R	-	C	R (including blood pressure)
ECG and echocardiogram	C	C	-	-	C
Assess for symptoms and signs of tumours	R	R	-	R	C
Abdominal ultrasound scan	R	R	R for tumour surveillance (except IC2 LOM cases)	-	-
Renal USS	(part of abdominal USS)	(part of abdominal USS)	-	C (if renal anomaly)	R

Molecular genetic analysis	R	R	-	-	C (if previous testing negative)
Offer contact details of BWS support group	R	R	-	R	R
Provide genetic counselling	R (to parents)	R (to parents)	-	C	R (alert young adult to future availability)
Refer to the specific consensus guideline if concerns identified in any area	R	R	R	R	R

R: recommend
C: consider depending on individual case
- : not applicable

Supplementary Figure 1: The performance of the "Consensus scoring system" compared to previously reported diagnostic criteria[9]. All clinical features that are part of the consensus scoring system were weighted accordingly and incorporated into the new model. Calculations were based on presence/absence of macrosomia, polyhydramnios/placentomegaly, hypoglycaemia, hemihypertrophy, macroglossia, facial naevus flammeus (simplex), ear lobe creases/pits, umbilical hernia/diastasis recti, nephromegaly/hepatomegaly, and embryonal tumours only.[9]

The consensus scoring system performs better than older diagnostic criteria (see figure 1 and ROC table) (though less well than the scoring system which was derived from the data used for the calculations[9]). For the sensitivity and specificity estimates (see below) Consensus(Diagnostic) refers to a consensus scoring system score of 4, whilst Consensus(For testing) refers to a score of 2, equating to probability thresholds of 0.21 and 0.13, respectively.



Area of ROC curves

Scoring system reference	**Area**	**95% CI**
New scoring system	0.819	0.794-0.845
Ibrahim *et al.*[12]	0.847	0.823-0.871
Elliott *et al*.[13]	0.762	0.732-0.791
Debaun & Tucker[15]	0.729	0.689-0.759
Weksberg *et al*.[183]	0.749	0.719-0.779
Zarate *et al*.[16]	0.687	0.655-0.720
Gaston *et al*.[9]	0.687	0.655-0.720

Sensitivities and specificities

	Sensitivity	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**
Consensus (Diagnostic)	63.4%	86.5%	80.4%	73.1%
Consensus (For testing)	92.2%	46.5%	60.0%	87.3%
Ibrahim *et al*.[12]	75.9%	81.8%	78.4%	79.6%
Elliott *et al*.[13]	43.5%	93.9%	86.2%	65.7%

DeBaun & Tucker[15]	83.5%	62.3%	65.8%	81.3%
Weksberg *et al*.[183]	74.4%	75.4%	72.5%	77.2%
Zarate *et al*.[16]	69.8%	82.5%	77.7%	75.8%
Gaston *et al*.[9]	43.3%	94.1%	86.5%	65.6%

BWS consensus: Biographies

Frédéric Brioude (1)

Frédéric Brioude is Associate Professor and Pediatric Endocrinologist at Armand Trousseau Hospital, Paris, France. He focuses on the clinical care and molecular diagnosis of Silver–Russell syndrome (SRS) and Beckwith–Wiedemann syndrome. He is a Member of the French Society for Pediatric Endocrinology and Diabetology. He has 20 PubMed publications, including papers on the discovery of CDKN1C mutations in SRS and a clinical study of multi-locus imprinting disturbance.

Jennifer M. Kalish (2)

Jennifer M. Kalish, MD, PhD is an Assistant Professor of Pediatrics 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 tumor formation. She co-authored the Clinical Cancer Research Pediatric Oncology Series guidelines and has published on the clinical spectrum of Beckwith-Wiedemann syndrome.

Alessandro Mussa (3)

Alessandro Mussa, MD, PhD: Staff phisitian at the NICU of the Città della Salute e della Scienza in Torino, Italy, Consultant of the Department of Pediatrics, Faculty of Medicine, Torino for the Clinics of Imprinting Disorders as an expert in their diagnosis and managment. Specific research interests in Beckwith-Wiedemann and Silver-Russell syndromes moslty focused in the clincal management and follow-up. Member of the Scientific Commitee of the Italian BWS Association and author of the Italian Recommendations for BWS. Author of over 70 publication in the field of pediatric endocrinology, metabolism and genetics and several papers on BWS.

Alison Foster (4)

Alison Foster is a doctoral research fellow in the Institute of Cancer and Genomic Sciences at the University of Birmingham 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 Bliek (5)

Jet Bliek 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 fetal alcohol syndrome. She has 44 publications including development and validation of novel diagnostic methods and epigenotype–phenotype correlations in imprinting disorders

Giovanni Battista Ferrero (6)

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 PUB MED 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 (7)

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 (TNDM) and Beckwith-Wiedemann syndrome (BWS) and describing the genotype-epigenotype–phenotype of these patients. She has 16 PubMed publications mainly on multi-locus imprinting disturbances.

Trevor Cole (8)

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

Robert Baker (9)

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

Monica Bertoletti (10)

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. Volunteer certified as an expert in youth communication, expertise in public relations and event organisation.

Guido Cocchi (11)

Guido Cocchi is Associate Professor, 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 (12)

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 Pediatric Oncology (SFCE). She focuses on the clinical care for pediatric solid tumors and lymphomas and is investigator in research programs on pediatric abdominal cancers (mainly neuroblastoma) and on late effects. She has over 100 PubMed publications across these topics.

Maurizio De Pellegrin (13)

Maurizio De Pellegrin MD graduated in Medicine at the University of Innsbruck (Austria), then worked at the Olgahospital Pediatric Center in Stuttgart (Germany), focusing on Paediatric Orthopaedics and Trauma. He finished his Residency Programme in Orthopedics at the University of Tübingen (Germany). Since 1989 he 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 Mucopolysaccaridosis and Prader-Willi, Down, Beckwith-Wiedemann and Moebius syndromes. Member of various Scientific Societies (Italian Society of Pediatric Orthopedics and Traumatology (SITOP), German Orthopedic Society (VKO), European Pediatric Orthopedics Society (EPOS), European Hip Society (EHS). Fields of major interest in Paediatric Orthopaedics: developmental dysplasia of the hip, pediatric foot deformities, congenital limb and spine deformities, rare diseases, limb lengthening, basic research of rare diseases

Khalid Hussain (14)

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 hyperinsulinemic hypoglycemia. He has published over 300 manuscripts in the field of childhood hypoglycaemia.

Abdulla Ibrahim (15)

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 (16)

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 (17)

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. In addition, her career focus is on basic and clinically applied research on the genetic aetiology of imprinting disorders, including Beckwith-Wiedemann syndrome. She has acted as the Polish Coordinator of UE Projects: DYSCERNE - A 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 (18)

Christian Kratz is full 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 is has launched a registry for patients with Li-Fraumeni syndrome and other cancer predisposition syndromes, including BWS. 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.

Dr Edmund J Ladusans (19)

Edmund Ladusans trained in Paediatric Cardiology at Guy's & Harefield Hospitals London. 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 M.D., Ph.D. (20)

Pablo Lapunzina M.D., Ph.D. is Director of INGEMM, Institute of Medical and Molecular Genetics, University Hospital La Paz, Autónoma University of Madrid, Spain. His focus is on dysmorphology, clinical genetics and specifically on 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 trained in Pediatrics and then in Medical Genetics and Dysmorphology. He also completed 3 years of training in Molecular Genetics. He is author of over 170 articles in the medical and scientific literature, 9 book chapters, and 5 books.

Yves Le Bouc (21)

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

Saskia Maas (22)

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 (23)

Fiona Macdonald is a graduate of Edinburgh University and carried out her PhD research at the University of Leicester. 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 (24)

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. 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 (25)

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 (26)

Sylvie Rossignol is Professor of Pediatrics at the Strasbourg University School of Medicine, France. She qualified in Paediatrics in 2003 and subsequently completed her fellowship in Pediatric Endocrinology at the department of “Explorations Fonctionnelles Endocriniennes” at the Trousseau Children Hospital in Paris, under the supervision of Pr Yves Le Bouc. She subsequently undertook research on the epigenetic regulation of the 11p15 region in Beckwith Wiedemann and Silver Russell syndromes in the associated INSERM unit. She obtained her PhD thesis at the Pierre et Marie Curie University, Paris , in 2008. Her research interests included prospective studies of growth and phenotype in BWS and SRS, molecular mechanisms of parental imprinting within the 11p15 region including the role of environment (especially ART) in the occurrence of the epigenetic defect.

Silvia Russo (27)

Silvia Russo is Group leader for diagnostic and research activities of rare Mendelian diseases and Imprinting Disturbances (Beckwith-Wiedemann-Silver Russell, Angelman/Prader-Willi, Cornelia de Lange X-linked Mental Retardation, including Fragile X and Rett Syndrome) and susceptibility to multifactorial pathologies, in particular Autism, Molecular Branch of the Cytogenetics and Molecular Genetics Laboratory, Istituto Auxologico Italiano, Milan. More than 800 BWS patients have been investigated in our laboratories testing all the known mechanisms, identifying the molecular mechanism in 249 unrelated patients. We collaborate in strict collaboration with clinician. Silvia is a Member of the Italian National BWS Association. Interested in epigenetic disorders and specially focused on mosaicism of imprinting disorders. She is also involved in research activity on the disease, aiming to disclose novel mechanisms at the basis of the syndrome by applying genomic tools (exome sequences, SNParray) and to investigate the origin of the epigenetic defects (Mutations in trans acting genes).

Caroleen Shipster (28)

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 (29)

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 publicaton in the field od pediatrics and genetics

Katrina Tatton-Brown (30)

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

Jair Tenorio (31)

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 (32)

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 (33)

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 oculocutanoeous 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 (34)

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

Raoul CM Hennekam (35)

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 (36)

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 Commitee 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 (37)

Zeynep Tümer is Professor and Chief of R&D, Applied Human Molecular Genetics, Kennedy Center, Rigshospitalet, University of Copenhagen, Denmark. She has 20 years' experience in classic and molecular cytogenetic analysis. She has been leader of microarray diagnostic facilities at the Kennedy Center since 2008 and leader of cytogenetics (Medical Genetics Clinic, ICMM, KU) for 4 years. Her main research interest is use of genomic technology (including array and next-generation sequencing strategies) to define genetic and/or epigenetic mechanisms of brain and/or neurological disorders such as Menkes disease, Tourette syndrome, intellectual disabilities, developmental and congenital disorders. She is a Board member of European Society of Human Genetics (ESHG) and Working Group Leader in COST Action BM1208 – EUCID.net on imprinting disorders. She has over 160 peer-reviewed publications spanning a broad range of human genetic disorders.

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