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Supplementary Information for

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Supplementary Table 1: Previously reported clinical criteria of BWSp from nine selected studies

Characteristic	Major	Minor	Estimated Prevalence in Spectrum[1–9]
Macroglossia	[1,3,10–12]		85%
Macrosomia (pre/post-natal overgrowth defined as >90th or >97th percentile)	[1,3,10–13]		67%
Abdominal wall defects General Exomphalos or umbilical hernia Exomphalos, diastasis recti or umbilical hernia Diastasis recti	[1,3,11–13] [10]	 [11,12]	General - 68 % Exomphalos – 44% Umbilical hernia – 44% Diastasis recti – 22 %
Organomegaly Nephromegaly	[1,11,12]	 [3]	General – 53% Nephromegaly – 38% Hepatomegaly – 37% Splenomegaly – 16%
Lateralised overgrowth	[11,12]	[1,3,13]	37%
Neonatal hypoglycaemia	[10]	[1,3,11–13]	51%
Facial naevus flammeus (simplex)		[1,3,11–13]	52%
Ear creases/pits	[10–12]	[1,3,13]	63%
Characteristic facial features (including midface underdevelopment, infraorbital creases, prominent mandible)		[11–13]	
Cardiac anomalies		[11–13]	20 %
Pregnancy-related findings (polyhydramnios, prematurity, enlarged placenta, thickened umbilical cord, placental mesenchymal dysplasia)		[11–13]	Polyhydramnios – 53%
Embryonal tumour	[11,12]		
Renal abnormalities	[11,12]		52%
Positive family history	[11,12]		
Cleft palate	[11,12]		3 %
Advanced bone age		[11,12]	
Polydactyly		[12]	3 %
Supernumerary nipples		[12]	

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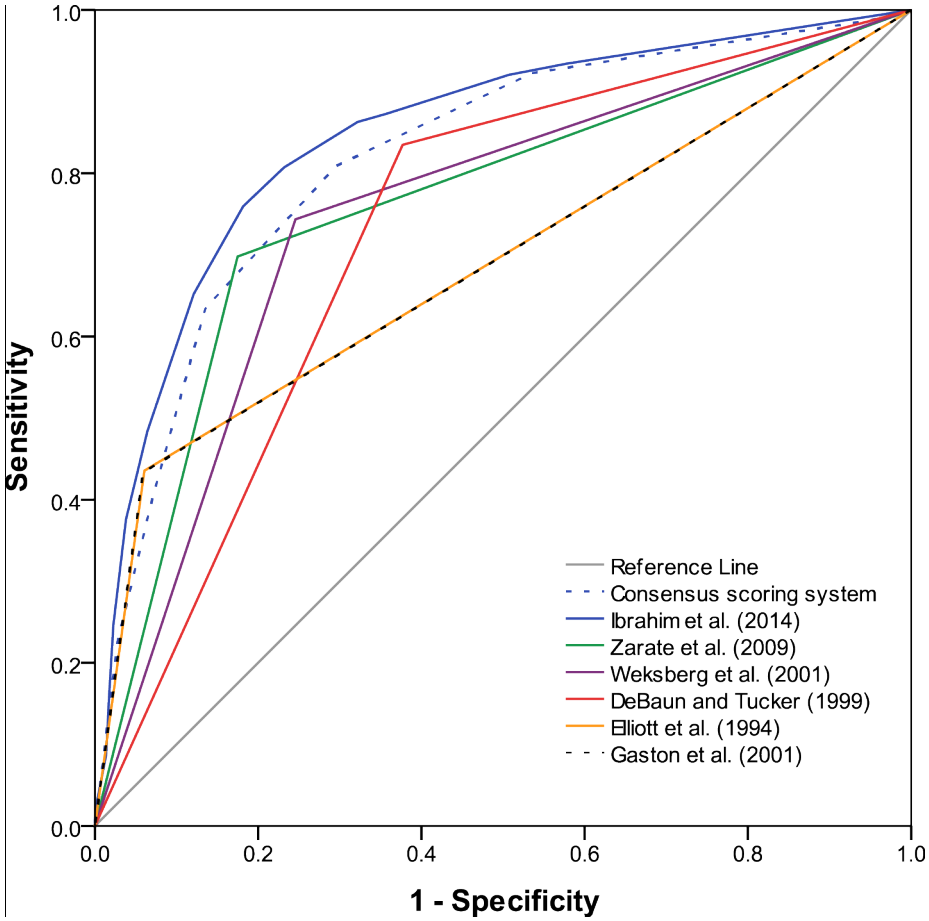
Supplementary Figure 1: The performance of the "Consensus scoring system" compared to previously reported diagnostic criteria. All clinical features that are part of the consensus scoring system were weighted accordingly and incorporated into the new model. Calculations were based on presence/absence 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.

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[1]). 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. Image reproduced from Ibrahim, A. *et al.* Methylation analysis and diagnostics of Beckwith-Wiedemann syndrome in 1,000 subjects. *Clin. Epigenetics* **6,** 11 (2014). under the Creative Commons License CC BY 4.0.



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Area of ROC curves

Scoring system reference	**Area**	**95% CI**
New scoring system	0.819	0.794-0.845
Ibrahim *et al.* [1]	0.847	0.823-0.871
Elliott *et al.* [2]	0.762	0.732-0.791
Debaun & Tucker[3]	0.729	0.689-0.759
Weksberg *et al.*[4]	0.749	0.719-0.779
Zarate *et al.*[5]	0.687	0.655-0.720
Gaston *et al.*[6]	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.*[1]	75.9%	81.8%	78.4%	79.6%
Elliott *et al.*[2]	43.5%	93.9%	86.2%	65.7%

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DeBaun & Tucker[3]	83.5%	62.3%	65.8%	81.3%
Weksberg *et al.*[4]	74.4%	75.4%	72.5%	77.2%
Zarate *et al.*[5]	69.8%	82.5%	77.7%	75.8%
Gaston *et al.*[6]	43.3%	94.1%	86.5%	65.6%

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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 intellectual 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	1
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, deeply set eyes, depressed nasal bridge, tented vermilion upper lip	2
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 intellectual	3

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			disability Cardiac anomalies, cardiomyopathy, arrhythmia Ulnar deviation Deep palmar and plantar creases 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 intellectual disability Scoliosis Seizures Cardiac anomalies Renal anomalies Neonatal hypotonia, jaundice and feeding difficulties Facial features: broad and prominent forehead, sparse frontotemporal hair, downslanting palpebral fissures, malar flushing, tall chin	4
Weaver syndrome	Autosomal dominant (frequent *de novo* mutations)	Mutation in *EZH2*	Tall stature Macrocephaly Variable intellectual disability Camptodactyly Soft/doughy skin Umbilical hernia Facial features: broad forehead, widely spaced eyes, pointed chin, macrotia and retrognathia in early childhood	5
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 intellectual disability Frequent autism and anxiety Hypotonia Brain anomalies	6

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			Slender body build Facial features: long face, prominent forehead, short nose, long philtrum, tall chin	
PTEN hamartoma tumour syndrome	Autosomal dominant	Mutation in *PTEN*	Prenatal overgrowth Macrocephaly Hypotonia Intellectual 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	[7]
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)	[8]

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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		1
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		2
Ectopic adrenocortical virilising adenoma Pancreatic cancer*	20 24*	Genome wide upd Genome wide upd*	Genome wide upd	Previous history of Wilms tumour	3 *Tenorio and Lapunzina (unpublished work).
Adrenal virilising adenoma	45	Loss of heterozygosity at HRAS (11p15.5)			4
Bilateral adrenal phaeochromocytoma	20	Not performed	Not recorded	Also history of bilateral breast adeno fibromas	5
Acute myeloid leukaemia	23	Not performed	Not recorded		6

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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	-	-

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			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