European Commission
Directorate-General for Health and Food Safety (DG SANTE)

ITHACA

ITHACA Board Meeting 2020

2020 December 11th

WG4 Guidelines parallel session

Development of syndrome specific guidelines: the First International Consensus Statement for Beckwith-Wiedemann syndrome

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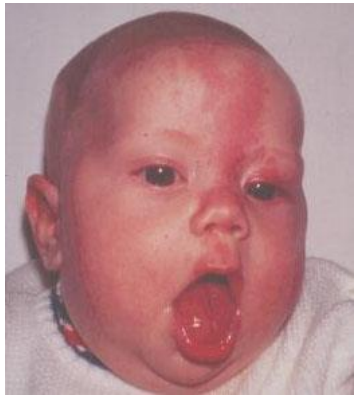
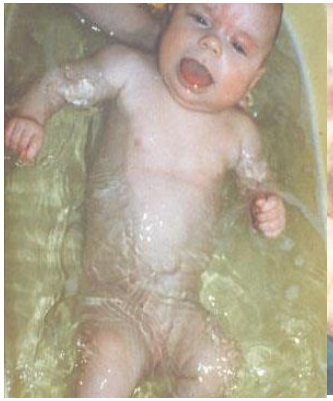
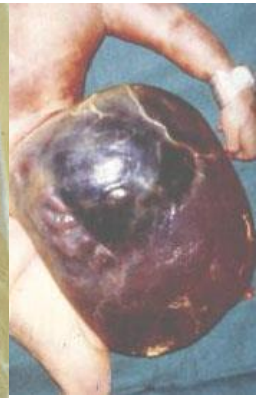
European Reference Networks

Beckwith-Wiedemann syndrome (BWS)

- Mostly sporadic (15% familial)
- Pre- and/or postnatal overgrowth, macroglossia and anterior abdominal wall defects
- Less commonly hypoglycaemia, ear creases, organomegaly, hemihypertrophy)
- ~5% of cases embryonal tumours
- Complex genetics: 11p15.5 epigenetic and genetic alterations
- Clinical and molecular overlaps with isolated hemihypertrophy and sporadic Wilms tumour
- Controversial topics:
  - Clinical definition and diagnostic criteria
  - Mode and extent of molecular testing
  - Tumour surveillance programmes: (different in USA and Europe)







European Network for Congenital Imprinting Disorders

- Established 2013
- Supported by COST (Action BM1208)
- Led by Thomas Eggermann (Aachen)
- Aimed to network clinicians, scientists, SMEs and patients in the field of Imprinting disorders
- Organised meetings, training schools, short term scientific missions, as well as patient-expert meetings.

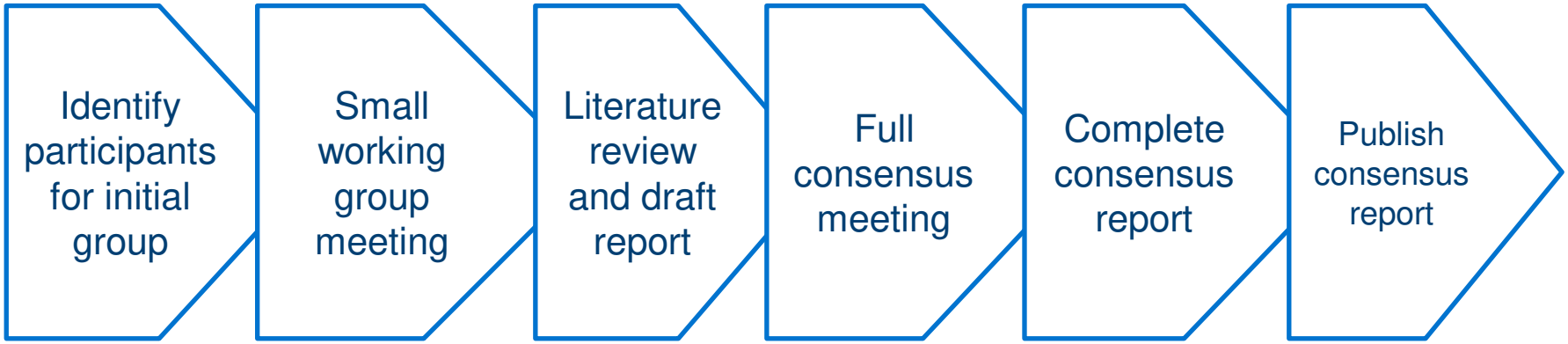
Activities included:

- Standardised nomenclature for imprinted loci/differentially methylated regions
- Consensus statement on Silver Russell syndrome
- Consensus statement on Beckwith-Wiedemann syndrome
- Consensus statement on Pseudohypoparathyroidism

COST Action

May 2015 Decision taken to hold EUCID sponsored Consensus Meeting

Eamonn Maher (UK), Andrea Riccio (Italy)



Beckwith Wiedemann Syndrome (BWS) pre-consensus meeting 25-26th February 2016

Birmingham, UK

11 partcipants

Day 1: 12pm – 5pm
Introductions and outline of consensus process
Review of Silver-Russell syndrome consensus experience and Italian BWS consensus
Clinical aspects and management
Clinical aspects and management continued

Day 2: 9am-1pm
Molecular aspects
Patient involvement
Review of preconsensus decisions, identification of key areas and individuals, action plan

Location

UK
Germany
Italy
France
Netherlands

Specialty

Clin Gen
Molec Gen
Paediatrics
PPI
Paed Endo
Paed Oncol

Decisions: BWS PreConsensus: Questions to be addressed

1. *Clinical Diagnostic issues and Incidence*
   Definition, clinical diagnostic criteria, frequency, environmental factors (e.g. Assisted Reproductive Technology)
2. *Molecular aetiology and clinical molecular diagnosis pathways*
   Genetic and epigenetic alterations, frequency and significance of multilocus methylation disturbance, which tests for clinical molecular diagnosis, diagnostic pathway etc.
3. Clinical aspects of BWS: natural history, management and genetics
   Manifestations of BWS in children and adults
   Prognosis and management of specific features
   Genotype-phenotype correlations are there
   Surveillance (e.g. embryonal tumours) and treatment
   Genetic counselling/Prenatal care
4. *Future perspectives: key questions for basic and clinical research*

Decisions: BWS PreConsensus: Who to invite?

1. *Specialties*

   Clinical Genetics, Molecular Genetics, Paediatrics, Paediatric Endocrinology, Patient group representation
   Plus
   Cardiology, obstetrics, paediatric oncology, orthopaedics, speech therapy, maxillofacial surgery, clinical psychology

2. *Representation*

   Geography
   - COST funding limited for non-Europe experts

   Nomination by specialist societies
   Patient group representation: EUCID patient expert group meeting held separately

Post PreConsensus Meeting Activities

1. Identify location and format for

500+ relevant publications identified

Each read and assessed for relevance to the three writing groups

2. *Three writing groups convened*

A. Clinical Diagnostic issues, Incidence, Environment etc.

B. Molecular aetiology and clinical molecular diagnosis pathways

C. Clinical aspects of BWS: natural history, management and genetics

- Each writing group had 2-3 lead writers and was free to recruit additional contributors
- Writing policy varied – few core writers + commenters versus many core writers
- 20 writers (~12 primary and 8 secondary) produced first draft consensus statement

Pre-Full Consensus Meeting Activities

1. *Decide format and location of full consensus meeting*
   - Over 3 days
   - Outside Paris
2. *Finalise invitee list*
   - Key experts?
   - Inclusivity?
   - Multidisciplinary?
   - Strong patient representation
3. *Financial support and sponsorship*
   - COST funding (approx. 30K)
   - No pharmaceutical funding
   - Successful application to medical charity (£5k)
   - Sponsorship of specialty group (nomination of representative)
4. *Distribute first draft consensus statement*

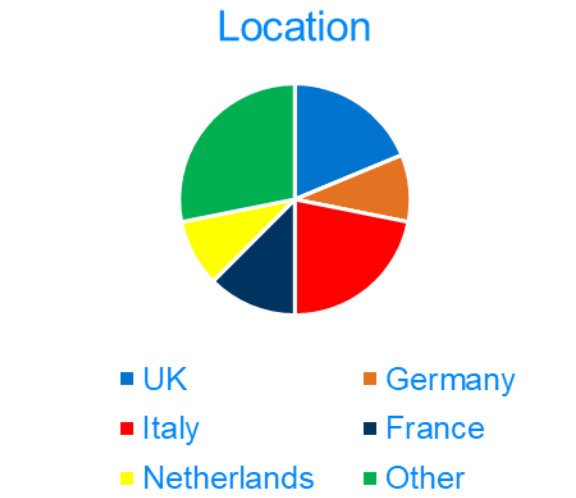
Full Consensus Meeting

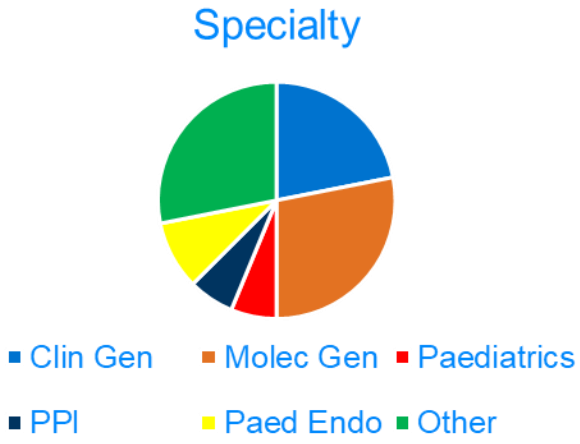
1. Location and format

Over 3 days
Lunch on Day 1 to Lunch on Day 3
"Isolated hotel" – evening meals on Days 1 and 2

2. *Attendees*

35 attendees





Full Consensus Meeting

Day One: Presentation of reports of first two working groups

Time	Chair	Topic	Content
20.03.2017			
13.00	Lunch		
14.00h	Maher, Brioude, Eggermann	Welcome, Organisation	Organisation, participants, voting
14.30h	Maher, Brioude, Khalish	Debate sessions	WG1 (clinical diagnosis) and WG2 (molecular diagnostics) presentations and discussion
16.00h	Break		
16.30h	Maher, Brioude, Riccio	Debate sessions	WG1 (clinical diagnosis) and WG2 (molecular diagnostics) presentations and discussions continued
19.30h	Dinner		

Full Consensus Meeting

Day Two Morning: Presentation of report of third working group

Time	Chair	Topic	Content
21.03.2017			
8.30h	Maher, Brioude, Mussa	Debate sessions	WG3 (management) presentations and discussion
10.30h	Break		
	Maher, Brioude, Mussa	Debate sessions	WG3 (management) presentations and discussion continued
12.30h	Lunch		

Full Consensus Meeting

Day Two Afternoon: Parallel discussions in individual working groups

Time	Chair	Topic	Content
21.03.2017			
12.30h	Lunch		
13.30h	Maher, Brioude, Khalish, Riccio	Separate WG1, WG2 and WG3 sessions	Individual working group discussions and refinement of consensus recommendations
15.00h	Break		
15.30h	Maher, Brioude, Khalish, Riccio	Separate WG1, WG2 and WG3 sessions	Individual working group discussions and refinement of consensus recommendations and consensus document revisions
17.30	Maher	"WG Writers" meeting	
19.30h	Dinner		

Preparation of consensus statements to be voted on – needed to be clear and precise

3.5 hours of intense detailed discussion
Creative solutions e.g. new definition of BWSp
Focused discussion of controversial topics (e.g. tumour surveillance)

Full Consensus Meeting

Day Three Morning: Voting on consensus recommendations

Time	Chair	Topic	Content
22.03.2017			
8.30h	Maher, Brioude, Riccio	Voting on consensus recommendations	WG1, WG2, WG3
10.30h	Break		
11.00h	Maher, Brioude, Riccio	Final approval of consensus recommendations	WG1, WG2, WG3
12.00h	Lunch (for those not transferring to ID school/Management meeting)		
13.00h	End		

Voting on consensus recommendations

Each recommendation (n=72) displayed, short discussion and then electronic voting

Anyone who was uncertain could abstain

Recommendations graded by approval rating:

Box 1 | **Details of the consensus voting process**

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

- A. Evidence or general agreement allow full agreement with the recommendation
- B. Evidence or general agreement are in favour of the recommendation
- C. Evidence or general agreement are weak for the recommendation
- D. There is not enough evidence or general agreement to agree with the recommendation

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

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

Voting on consensus recommendations

R	Recommendation	Strength of recommendation
Management of renal complications		
51	At diagnosis of BWSp, all patients should be screened for nephro-urological malformations by clinical evaluation and USS	A+++
52	Physicians should be aware of the possibility of hypercalciuria, which can lead to nephrocalcinosis	A++
53	Patients with USS-detected anomalies should be referred to a paediatric nephrologist and urologist for specific follow-up	A+++
54	For patients undergoing abdominal surveillance for tumour screening, physicians and radiologists should pay attention to the possibility of nephrocalcinosis and/or stones	A+++
55	For patients with BWSp, at the time of adult transition, a nephro-urological evaluation (clinical examination, blood pressure and USS) should be performed	A++
BWSp and embryonal tumours		
56	Screening should be stratified according to the genotype	A+++
57	Abdominal USS for BWSp-related tumours every 3 months until age 7 years is recommended for all patients with BWSp except patients with isolated IC2 LOM	A++
58	For patients with BWSp and upd(11)pat, abdominal USS for Wilms tumour and hepatoblastoma every 3 months until age 7 years is recommended	A+++
59	For patients with BWSp and IC1 GOM, abdominal USS for Wilms tumour every 3 months until age 7 years is recommended	A+++
60	For patients with BWSp and IC2 LOM, no tumour surveillance is recommended	*A/B+
61	For patients with BWSp and a *CDKN1C* mutation, abdominal USS for neuroblastoma every 3 months until age 7 years is recommended	A+

Consensus innovations

Box 2 | **Clinical features of Beckwith–Wiedemann spectrum**

Cardinal features (2 points per feature)

- Macroglossia
- Exomphalos
- Lateralized overgrowth
- Multifocal and/or bilateral Wilms tumour or nephroblastomatosis
- Hyperinsulinism (lasting >1 week and requiring escalated treatment)
- Pathology findings: adrenal cortex cytomegaly, placental mesenchymal dysplasia or pancreatic adenomatosis

Suggestive features (1 point per feature)

- Birthweight >2 SDS above the mean
- Facial naevus simplex
- Polyhydramnios and/or placentomegaly
- Ear creases and/or pits
- Transient hypoglycaemia (lasting <1 week)
- Typical BWSp tumours (neuroblastoma, rhabdomyosarcoma, unilateral Wilms tumour, hepatoblastoma, adrenocortical carcinoma or phaeochromocytoma)
- Nephromegaly and/or hepatomegaly
- Umbilical hernia and/or diastasis recti

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

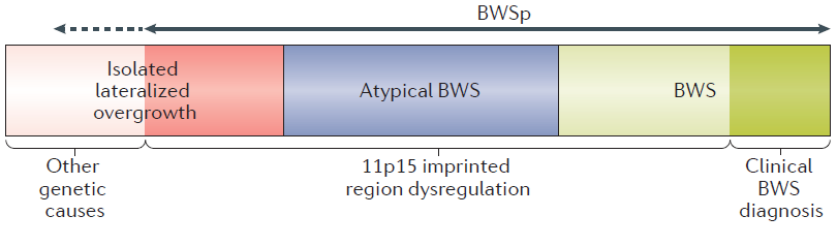


Figure 1 | **The Beckwith–Wiedemann spectrum.** The consensus group introduced the concept of the Beckwith–Wiedemann spectrum (BWSp), which includes patients with a clinical diagnosis of Beckwith–Wiedemann syndrome (BWS) with or without an (epi) genetic change at the BWS locus on chromosome 11p15, patients with 'atypical BWS' (defined as fewer cardinal and suggestive features than those needed for a clinical diagnosis of BWS) and an (epi)genetic change at the BWS locus, and patients with 'isolated lateralized overgrowth' and an (epi)genetic change at the BWS locus. The dotted arrow indicates that some patients with apparent isolated lateralized overgrowth and no 11p15 abnormality might subsequently be found to have an 11p15 abnormality on testing of additional tissues or with a more sensitive assay. Patients with clinical BWS and no detectable 11p15 abnormality might be further investigated with additional clinical evaluation and consideration of other syndromes, which may have features overlapping with BWSp, and appropriate testing for those syndromes may be warranted.

"Final steps"

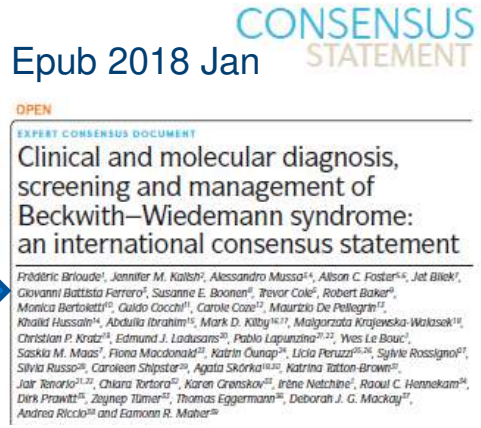
- Revise draft consensus report and prepare for submission (reduce word count by ~two thirds)
- Post-consensus analysis showed that new diagnostic criteria performed well compared to other proposed diagnostic criteria
- Presubmission enquiry to Nat Rev Endocrinology elicited encouraging response

Preconsensus meeting Feb 2016

Consensus meeting Mar 2017

Manuscript submitted August 2017

Epub 2018 Jan


CONSENSUS STATEMENT

OPEN

EXPERT CONSENSUS DOCUMENT

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

Dec 2020: 104 citations

BWS Consensus: Conclusions

Overall worked well despite complexities of disorder and controversial topics

Enthusiastic and collaborative participants

F2F meeting crucial to developing new diagnostic concepts and reaching agreement on controversial topics

Videoconferencing would now be part of our plans (e.g first meeting)

Funding from EU Cost Action was fundamental to success

Post-consensus work to disseminate the consensus findings and ensure national adoption of recommendation requires substantial effort

Acknowledgements

EXPERT CONSENSUS DOCUMENT

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

Frédéric Brioude[1], Jennifer M. Kalish[2], Alessandro Mussa[3,4], Alison C. Foster[5,6], Jet Bliek[7], Giovanni Battista Ferrero[8], Susanne E. Boonen[9], Trevor Cole[5], Robert Baker[5], Monica Bertoletti[10], Guido Cocchi[11], Carole Cooe[12], Maurizio De Pellegrin[13], Khalid Hussain[14], Abdulla Ibrahim[15], Mark D. Kilby[16,17], Malgorzata Krajewska-Walasek[18], Christian P. Kratz[19], Edmund J. Ladusans[20], Pablo Lapunzina[21,23], Wes Le Bouc[1], Saskia M. Maas[7], Fiona Macdonald[23], Katrin Õunap[24], Licia Peruzzi[25,26], Sylvie Rossignol[27], Silvia Russo[28], Caroleen Shipster[29], Agata Skórka[18,30], Katrina Tatton-Brown[31], Jair Tenorio[21,22], Chiara Tortora[32], Karen Grønskov[33], Irène Netchine[1], Raoul C. Hennekam[34], Dirk Prawitt[35], Zeynep Tümer[33], Thomas Eggermann[36], Deborah J. G. Mackay[37], Andrea Riccio[38] and Eamonn R. Maher[39]

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