Endo-ERN

European Reference Network
on Rare Endocrine Conditions

# General Assembly

## Day 2

## Virtual meeting

Wednesday 16 February 2022, 10:00 – 11:30 hrs

European Commission | Endo-ERN is a European Reference Network co-funded by the European Union's Health Programme under grant agreement No 739572

European Reference Network

# programme: Wednesday 16 February 2022

| | |
|---|---|
| **10:00 – 10:15** | **Guidelines & Publications**<br>*Anna Nordenström* (WP4 chair) &<br>*Jérôme Bertherat* (Endo-ERN Publication Committee) |
| **10:15 – 10:30** | **Harmonisation and networking for Endo-ERN reference labs**<br>*Anders Juul* (WP5 chair) & *Emily White* (Endo-ERN Coordination Team) |
| **10:30 – 10:45** | **Coffee / Tea Break** |
| **10:45 – 11:05** | **Update from the continuously evolving Endo-ERN ePAGs** |
| **11:05 – 11:25** | **Alignment with ESE / ESPE**<br>*Nicole Reisch* (ESE representative)<br>*Faisal Ahmed* (ESPE representative) |
| **11:25 – 11:30** | **Round Up** |
| **11:30 – 12.30** | **Lunch Break** |

| | |
|---|---|
| | Meet and interact with your MTG co-workers |
| 12:30 – 13:00 | MTG5 Growth & Genetic Obesity Syndromes |
| 13:10 – 13:40 | MTG6 Pituitary |
| 13:50 – 14:20 | MTG7 Sex Development & Maturation |
| 14:30 – 15:00 | MTG8 Thyroid |

# Guidelines

**Anna Nordenström**

# ERN Guideline update

- EU – Spanish consortium, SANTE, to facilitate guideline work
- Ambitious program,
  - Instructions 12 chapters
  - Web-based courses
- Proposed overaching guideline panel
- Also controversial because of the lack of funding to the ERN's
  - Courses were made optional

- Overview of guidelines on the Endo-ERN webpage
  - with links under each MTG

# ERN Guideline update

- **Pubertal induction and transition to adult sex hormone replacement in patients with pituitary or gonadal reproductive hormone deficiency. An Endo-ERN clinical practice guideline.**
- Nordenström A, Ahmed SF, van den Akker E, Blair J, Bonomi M, Brachet C, Broersen LHA, Claahsen H, Dessens AB, Gawlik A, Gravholt CH, Juul A, Krausz C, Raivio, T, Smyth A, Touraine P, Vitali D, Dekkers OM

- Manuscript submitted
- ESPE, ESE and EAA have endorsed the guideline
- 5 reviewers have given their feed-back

- ePAG meeting on Guideline involvement, Ilaria Galletti invited
- Lay version will be produced in several languages

# ERN Guideline update

- **Congenital Hypothyroidism: A 2020-2021 Consensus Guideline Update – An EdnoERN initiative endorsed by the ESPE and ESE**
- van Trotsenburg P, Stoupa A, Léger J, Rohrer T, Peters C, Fugazzola L, Cassio A, Heinrichs C, Beauloye V, Pohlenz J, Rodien P, Coutant R, Szinnai G, Murray P, Bartés B, Luton D, Salerno M, de Sanctis L, Vigone M, Krude H, Persani L, Polak M
- Published in Thyroid 2021 Mar;31(3):387-419

- **Familial hypoaldosteronism**
- Ongoing

- More guidelines to come

# Publications

George Mastorakos

# Endo-ERN Publication Committee

Pr. Jerome BERTHERAT
Pr. Violeta IOTOVA
Pr. George MASTORAKOS

**Citation of publications generated within Endo-ERN**
**AND**
**Citation for publications not directly funded or written by Endo-ERN and include authorship of Endo-ERN members**

**Special supplement in *Endocrine Connections***

European Reference Network

# Citation of publications generated within Endo-ERN

## Endo-ERN: Guidance On The Role of Authors and Contributors

This guidance is intended to ensure that contributors making substantive contributions to studies designed and executed under the umbrella of Endo-ERN are given due credit and that they understand their roles and responsibilities in being held accountable for future publications.

## Recommended text & logos for Endo-ERN related scientific communications

**Acknowledgement of funding**

This work is generated within

This work is supported (not financially) by

This project has received support from

the European Reference Network on Rare Endocrine Conditions (Endo-ERN) – Project ID No 739572. Endo-ERN is co-funded by the European Union within the framework of the 3rd Health Programme. *Endo-ERN is also supported by the European Society of Endocrinology and the European Society for Paediatric Endocrinology.*

**Acknowledgement of assistance of Reference Centres within Endo-ERN**

We would like to acknowledge the support of the following reference centres that participate in the European Reference Network on Rare Endocrine Conditions (Endo-ERN):

(list reference centres alphabetically by country)
[list available at https://endo-ern.eu/about/reference-centres/]

European Reference Network

# Publication Committee Proposal for Citation for publications not directly funded or written by Endo-ERN and include authorship of Endo-ERN members

**Issue:** There is no means to formally acknowledge already existing literature **not directly funded or written by Endo-ERN**

**Aim:** To create formal **criteria to publicly endorse publications from CPGs** such as reliable **best practice guidelines** (useful in clinical practice to our members and for educational purposes).

*Proposed criteria listed on the right (using EuroBloodNet guide as a map)*

**a) Origin of Publication**

- **Created by an (affiliated) scientific partner of Endo ERN**
- **Methodology adopted** e.g. GRADE, Delphi method etc.

**b) Authors**

- **At least 2 authors** from member states/members of Endo-ERN

**c) Scope & Purpose**

a. Prevention
b. Diagnosis
c. Treatment

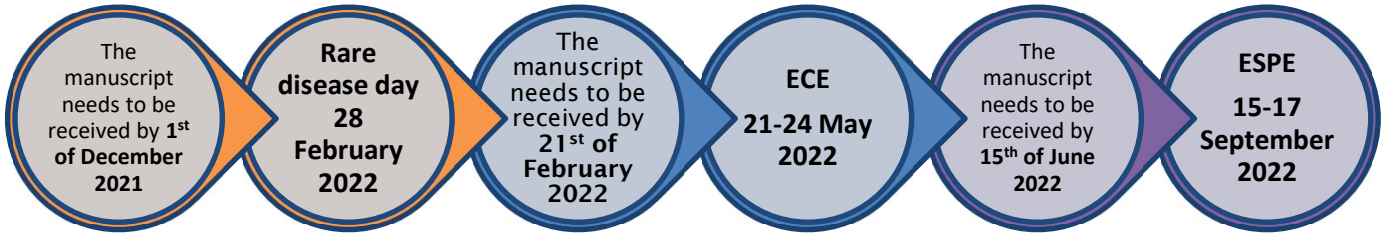
**d) Compliance to ERN Indicators**

- Comply with v7.5
- All data/trial registration standards met
- **Approved by PC of Endo ERN**

European Reference Network

# Special supplement in *Endocrine Connections*

The Endo-ERN special supplemental issue of **Endocrine Connections (Editor-In-Chief: Prof. Adrian J.L. Clark)** will appear online within 2022 and will include manuscripts submitted (proposed by MTGs and WPs) within 3 different deadlines to appear online on **specific dates** related to **special events**:




**Articles to be published on Rare Disease Day**:

1. Endo-ERN in its 5th year – a pinch of care, science, curiosity and new horizons
2. Understanding and preventing transition drop-out among adolescents and young adults with rare endocrine disorders

# Harmonisation and networking for Endo-ERN reference labs

**Anders Juul & Emily White**

WP5: Diagnostics and Laboratory Analysis

George Mastorakos, Trine Holm Johannsen and Anders Juul

# Publications

## PUBLICATIONS

- **Johannsen TH, Andersson AM, Ahmed SF, de Rijke YB, Greaves RF, Hartmann MF, Hiort O, Holterhus PM, Krone NP, Kulle A, Ljubicic ML, Mastorakos G, McNeilly J, Pereira AM, Saba A, Wudy SA, Main KM, and Juul A.** Peptide hormone analysis in diagnosis and treatment of Differences of Sex Development: joint position paper of EU COST Action 'DSDnet' and European Reference Network on Rare Endocrine Conditions. European Journal of Endocrinology 2020; 182: P1-P15.

- **Eggermann T, Elbracht M, Kurth I, Juul A, Johannsen TH, Netchine I, Mastorakos G, Johannsson G, Musholt TJ, Zenker M, Prawitt D, Pereira AM, and Hiort O.** Genetic testing in inherited endocrine disorders: joint position paper of the European reference network on rare endocrine conditions (Endo-ERN).; European Reference Network on Rare Endocrine Conditions (ENDO-ERN). Orphanet Journal of Rare Diseases 2020; 15: 144.

- **Johannsen TH, Ljubicic ML, Young J, Trabado S, Petersen JH, Linneberg A, Albrethsen J, and Juul A.** Serum Insulin-like Factor 3 Quantification by LC-MS/MS in Male Patients with Hypogonadotropic Hypogonadism and Klinefelter Syndrome. *Endocrine 2021.*

- **Mönig I, Steenvoorden D, de Graaf JP, Ahmed SF, Taruscio D, Johannsen TH, Juul A, Beun JG, Hiort I, and Pereira AM.** CPMS – improving patient care in Europe via virtual case discussions. *Endocrine 2021.*

- **Persani L, Bonomi M, Cools M, Dattani M, Dunkel L, Gravholt CH, Juul A.** ENDO-ERN expert opinion on the differential diagnosis of pubertal delay. *Endocrine 2021.*

- **Mönig I, Hoppmann J, Johannsen TH, Juul A, Werner R, Lünstedt R, Birnbaum W, Marshall L, Wünsch L, Hiort O.** Pubertal development in 46,XY patients with NR5A1 mutations. *Endocrine 2021.*

# Publications WP5

REVIEW Open Access

## Genetic testing in inherited endocrine disorders: joint position paper of the European reference network on rare endocrine conditions (Endo-ERN)

Thomas Eggermann[1*], Miriam Elbracht[1], Ingo Kurth[1], Anders Juul[2,3], Trine Holm Johannsen[2,3], Irène Netchine[4], George Mastorakos[5], Gudmundur Johannsson[6], Thomas J. Musholt[7], Martin Zenker[8], Dirk Prawitt[9], Alberto M. Pereira[10], Olaf Hiort[11] and on behalf of the European Reference Network on Rare Endocrine Conditions (ENDO-ERN

**Abstract**

**Background:** With the development of molecular high-throu knowledge on the contribution of genetic and epigenetic alt has massively expanded. However, the rapid implementation makes the interpretation of diagnostic data increasingly comp

**Main body:** This joint paper of the ENDO-ERN members ai relevance of comprehensive genetic diagnostic testing in r molecular diagnosis. This early diagnosis of a genetically b management and helps the patients and their families in t identification of a causative (epi)genetic alteration allows a planning as the basis of genetic counselling. Asymptomati prenatal testing might be offered, where appropriate.

**Conclusions:** The decision on genetic testing in the diagn on their appropriateness to reliably detect the disease-caus value, and cost-effectiveness. The future assessment of dat in interdisciplinary discussions using all available clinical an

**Keywords:** Rare endocrine conditions, Genetic testing, Imp homeostasis - Hypogonadotropic hypogonadism - differen

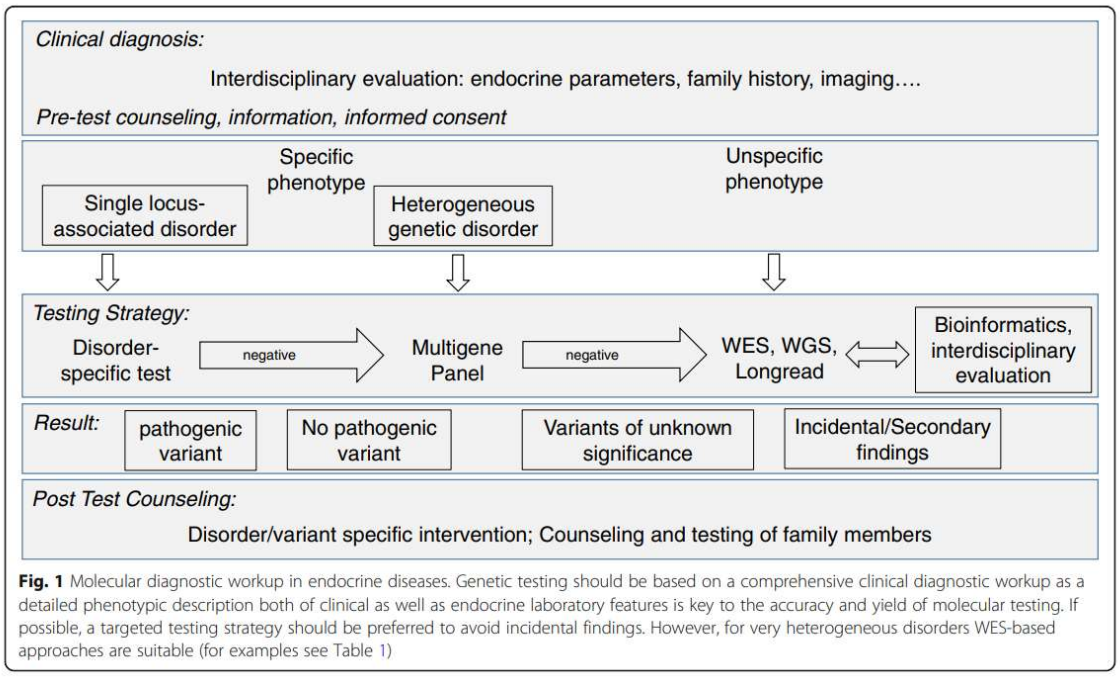



**Fig. 1** Molecular diagnostic workup in endocrine diseases. Genetic testing should be based on a comprehensive clinical diagnostic workup as a detailed phenotypic description both of clinical as well as endocrine laboratory features is key to the accuracy and yield of molecular testing. If possible, a targeted testing strategy should be preferred to avoid incidental findings. However, for very heterogeneous disorders WES-based approaches are suitable (for examples see Table 1)

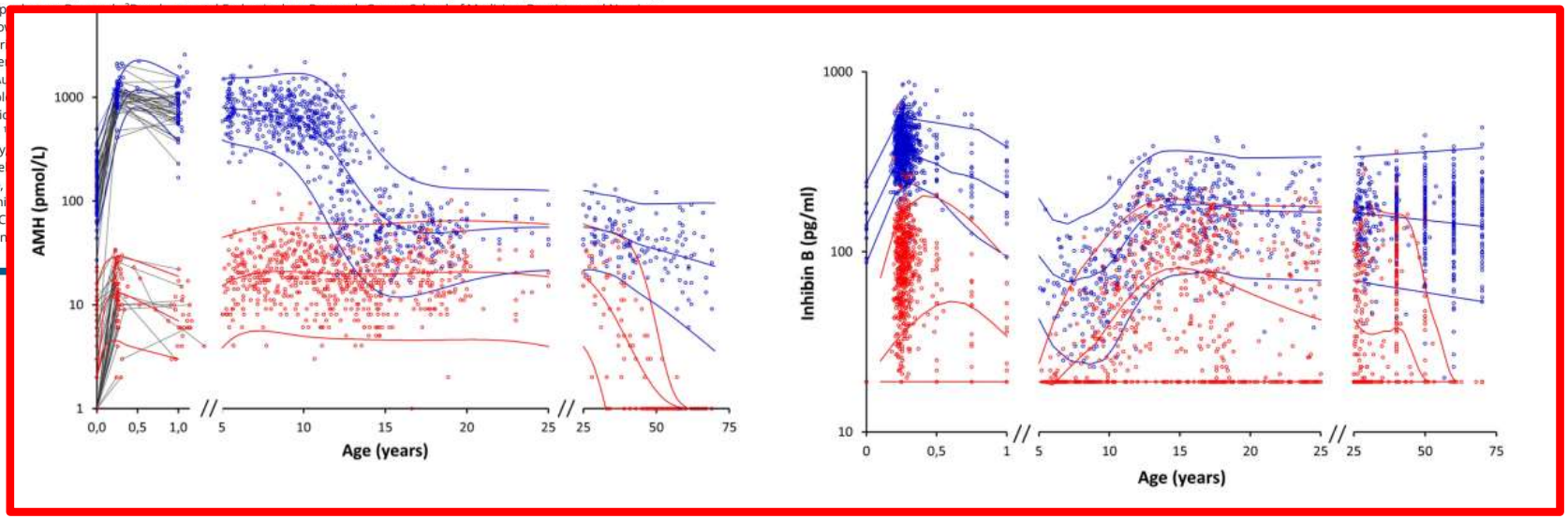
# Publications WP5

**Consensus Statement** | T H Johannsen and others | Peptide hormones and DSD | **182**:6 | **P1**–P15

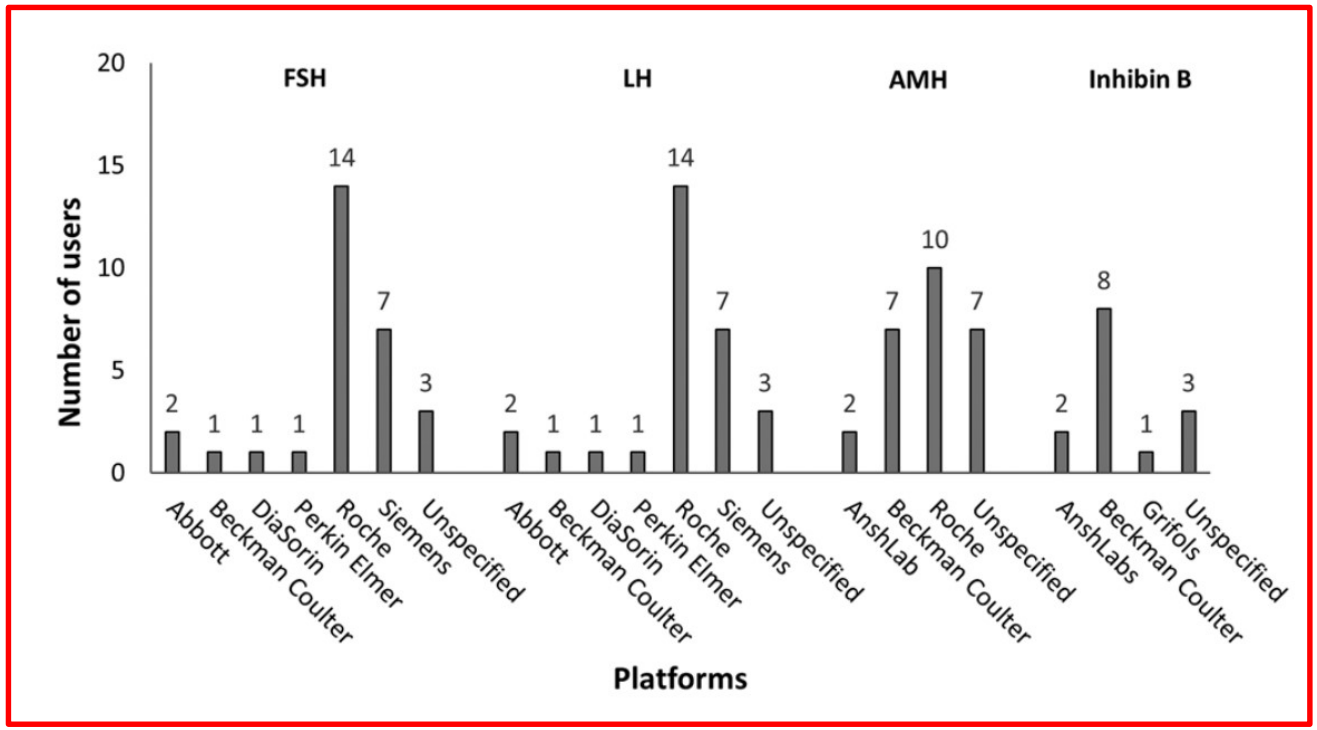
## Peptide hormone analysis in diagnosis and treatment of Differences of Sex Development: joint position paper of EU COST Action 'DSDnet' and European Reference Network on Rare Endocrine Conditions

**T H Johannsen[1,2], A-M Andersson[1,2], S F Ahmed[3], Y B de Rijke[4], R F Greaves[5,6,7], M F Hartmann[8], O Hiort[9], P-M Holterhus[10], N P Krone[11], A Kulle[10], M L Ljubicic[1,2], G Mastorakos[12], J McNeilly[13], A M Pereira[14], A Saba[15], S A Wudy[8], K M Main[1,2]** and **A Juul[1,2] on behalf of Working Group 3 'Harmonisation of Laboratory Assessment' of the European Cooperation in Science** and **Technology (COST) Action BM1303 'DSDnet'** and **Work Package 5 'Diagnostics** and **Laboratory Analysis' of the European Reference Network on Rare Endocrine Conditions**

[1]Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [2]International Center for Research and Research Training in Endocrine Disruption of Male Reproduction and Child Health (EDMaRC), Rigshospitalet, University of Copenhagen, Cop
University of Glasgo
Netherlands, [5]Victor
and Biomedical Scie
Parkville, Victoria, A
Pediatric Endocrinol
[9]Division of Pediatri
Luebeck, Germany,
Albrechts-University
University of Sheffie
Faculty of Medicine,
Queen Elizabeth Uni
University Medical C
Critical Care Medicin



# Publications WP5



# Publications WP5

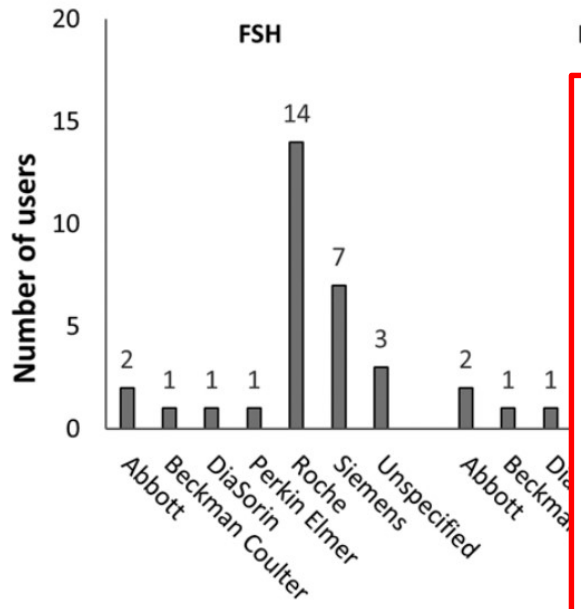
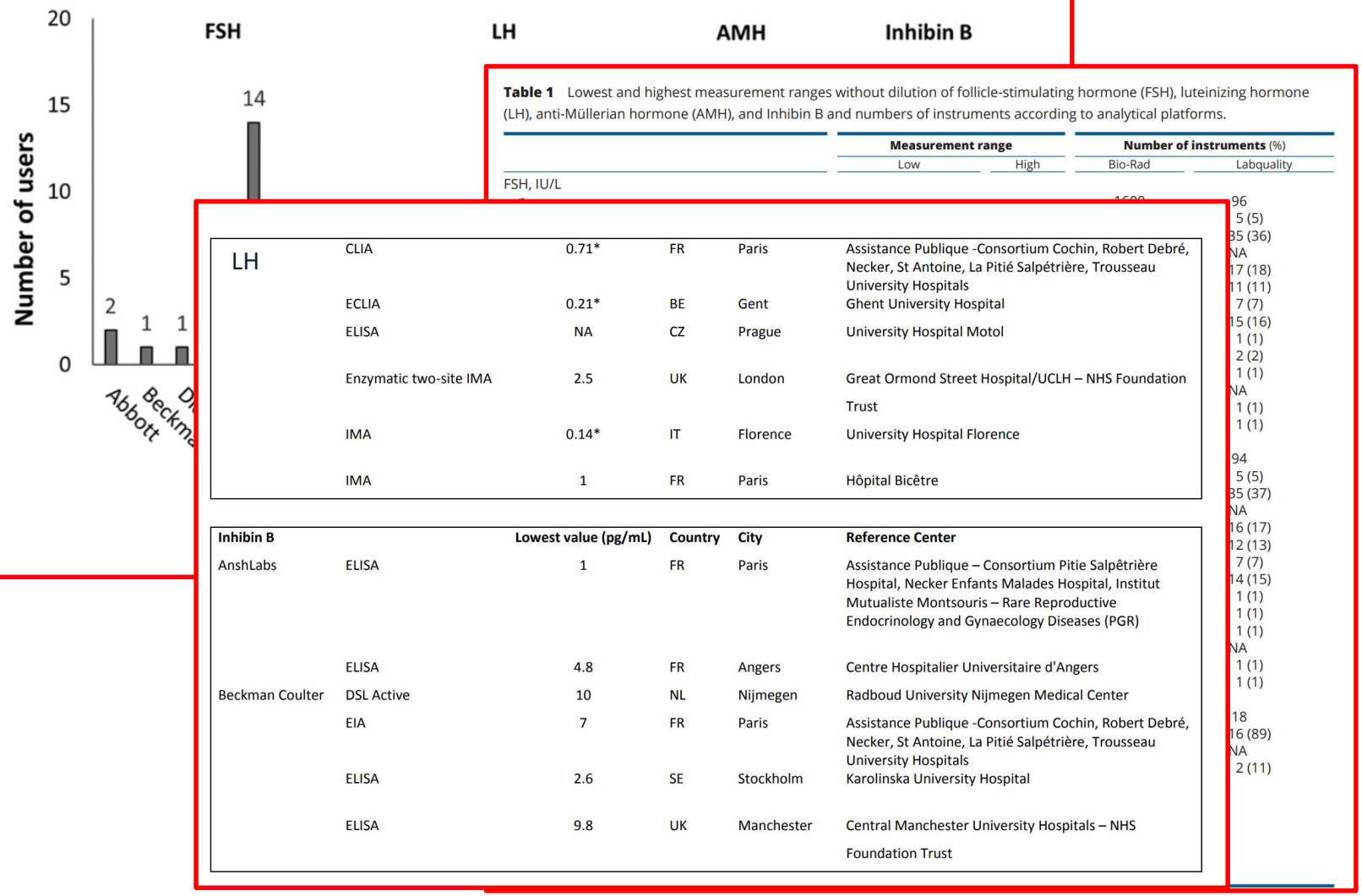



**Table 1** Lowest and highest measurement ranges without dilution of follicle-stimulating hormone (FSH), luteinizing hormone (LH), anti-Müllerian hormone (AMH), and Inhibin B and numbers of instruments according to analytical platforms.

| | Measurement range | | Number of instruments (%) | |
|---|---|---|---|---|
| | Low | High | Bio-Rad | Labquality |
| FSH, IU/L | | | | |
| *n* | | | 1600 | 96 |
| Roche Elecsys & Cobas e411* | 0.10 | 200 | 269 (17) | 5 (5) |
| Roche Modular E & Cobas e601-e801 | 0.1 (e801: 0.3) | 200 | 19 (1) | 35 (36) |
| Roche Cobas 6000 & Cobas 8000 | 0.1 | 200 | 291 (18) | NA |
| Siemens Advia Centaur | 0.3 | 200 | 300 (19) | 17 (18) |
| Siemens Immulite | 0.1 | 170 | 53 (3) | 11 (11) |
| Siemens Dimension Vista | 0.2 | 200 | 5 (0.3) | 7 (7) |
| Abbott Architect | 0.05 | 150 | 305 (19) | 15 (16) |
| Beckman Coulter Access & Unicel DxI | 0.2 | 200 | 168 (11) | 1 (1) |
| bioMérieux Vidas Group | 0.1 | 110 | 80 (5) | 2 (2) |
| Vitros Systems | 0.66 | 200 | 49 (3) | 1 (1) |
| Tosoh | 0.1 | 250 | 27 (2) | NA |
| DiaSorin Liaison | 0.25 | 400 | 15 (1) | 1 (1) |
| Perkin Elmer AutoDelfia | 0.05 | 256 | 1 (0.1) | 1 (1) |
| LH, IU/L | | | | |
| *n* | | | 1601 | 94 |
| Roche Elecsys & Cobas e411* | 0.10 | 200 | 260 (16) | 5 (5) |
| Roche Modular E & Cobas e601-e801 | 0.1 (e801: 0.3) | 200 | 18 (1) | 35 (37) |
| Roche Cobas 6000 & Cobas 8000 | 0.10 | 200 | 301 (19) | NA |
| Siemens Advia Centaur | 0.1 | 200 | 304 (19) | 16 (17) |
| Siemens Immulite | 0.05 | 200 | 52 (3) | 12 (13) |
| Siemens Dimension & Vista | 0.2 | 150 | 6 (0.4) | 7 (7) |
| Abbott Architect | 0.09 | 250 | 299 (19) | 14 (15) |
| Beckman Coulter Access & Unicel DxI | 0.2 | 250 | 167 (10) | 1 (1) |
| bioMérieux Vidas Group | 0.1 | 100 | 81 (5) | 1 (1) |
| Vitros Systems | 0.216 | 200 | 50 (3) | 1 (1) |
| Tosoh | 0.1 | 250 | 26 (2) | NA |
| DiaSorin Liaison | 0.2 | 250 | 14 (1) | 1 (1) |
| Perkin Elmer AutoDelfia | 0.05 | 250 | 1 (0.1) | 1 (1) |
| AMH, pmol/L | | | | |
| *n* | | | 99† | 18 |
| Roche Elecsys/Cobas | 0.071 | 164.2 | 44 (44) | 16 (89) |
| Beckman Coulter Access | 0.14 | 171 | 28 (28) | NA |
| Beckman Coulter AMH Gen II | 0.57 | 160.7 | 24 (24) | 2 (11) |
| INHIBIN B, pg/mL | | | | |
| Beckman Coulter Inhibin Gen II ELISA | 7 | 1000 | | |
| DSL** | 7 | 1000 | | |
| Serotec** | 15 | 1000 | | |
| Oxford Bio-Innovation Ltd.** | 15 | 1000 | | |
| ANSH LABS Inhibin B ELISA AL-107 (RUO) | 1.6 | 1390 | | |

# Publications WP5

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| | | Low | High | Bio-Rad | Labquality |
| FSH, IU/L | | | | | |
| | | | | | 96 |
| | | | | | 5 (5) |
| | | | | | 35 (36) |
| | | | | | NA |
| | | | | | 17 (18) |
| | | | | | 11 (11) |
| | | | | | 7 (7) |
| | | | | | 15 (16) |
| | | | | | 1 (1) |
| | | | | | 2 (2) |
| | | | | | 1 (1) |
| | | | | | NA |
| | | | | | 1 (1) |
| | | | | | 1 (1) |
| | | | | | 94 |
| | | | | | 5 (5) |
| | | | | | 35 (37) |
| | | | | | NA |
| | | | | | 16 (17) |
| | | | | | 12 (13) |
| | | | | | 7 (7) |
| | | | | | 14 (15) |
| | | | | | 1 (1) |
| | | | | | 1 (1) |
| | | | | | 1 (1) |
| | | | | | NA |
| | | | | | 1 (1) |
| | | | | | 1 (1) |
| | | | | | 18 |
| | | | | | 16 (89) |
| | | | | | NA |
| | | | | | 2 (11) |

| LH | | | | | |
|---|---|---|---|---|---|
| | CLIA | 0.71* | FR | Paris | Assistance Publique -Consortium Cochin, Robert Debré, Necker, St Antoine, La Pitié Salpétrière, Trousseau University Hospitals |
| | ECLIA | 0.21* | BE | Gent | Ghent University Hospital |
| | ELISA | NA | CZ | Prague | University Hospital Motol |
| | Enzymatic two-site IMA | 2.5 | UK | London | Great Ormond Street Hospital/UCLH – NHS Foundation Trust |
| | IMA | 0.14* | IT | Florence | University Hospital Florence |
| | IMA | 1 | FR | Paris | Hôpital Bicêtre |

| Inhibin B | | Lowest value (pg/mL) | Country | City | Reference Center |
|---|---|---|---|---|---|
| AnshLabs | ELISA | 1 | FR | Paris | Assistance Publique – Consortium Pitie Salpêtrière Hospital, Necker Enfants Malades Hospital, Institut Mutualiste Montsouris – Rare Reproductive Endocrinology and Gynaecology Diseases (PGR) |
| | ELISA | 4.8 | FR | Angers | Centre Hospitalier Universitaire d'Angers |
| Beckman Coulter | DSL Active | 10 | NL | Nijmegen | Radboud University Nijmegen Medical Center |
| | EIA | 7 | FR | Paris | Assistance Publique -Consortium Cochin, Robert Debré, Necker, St Antoine, La Pitié Salpétrière, Trousseau University Hospitals |
| | ELISA | 2.6 | SE | Stockholm | Karolinska University Hospital |
| | ELISA | 9.8 | UK | Manchester | Central Manchester University Hospitals – NHS Foundation Trust |

# Publications WP5

Endocrine (2021) 71:578–585
https://doi.org/10.1007/s12020-021-02609-0

ORIGINAL ARTICLE

## Serum insulin-like factor 3 quantification by LC–MS/MS in male patients with hypogonadotropic hypogonadism and Klinefelter syndrome

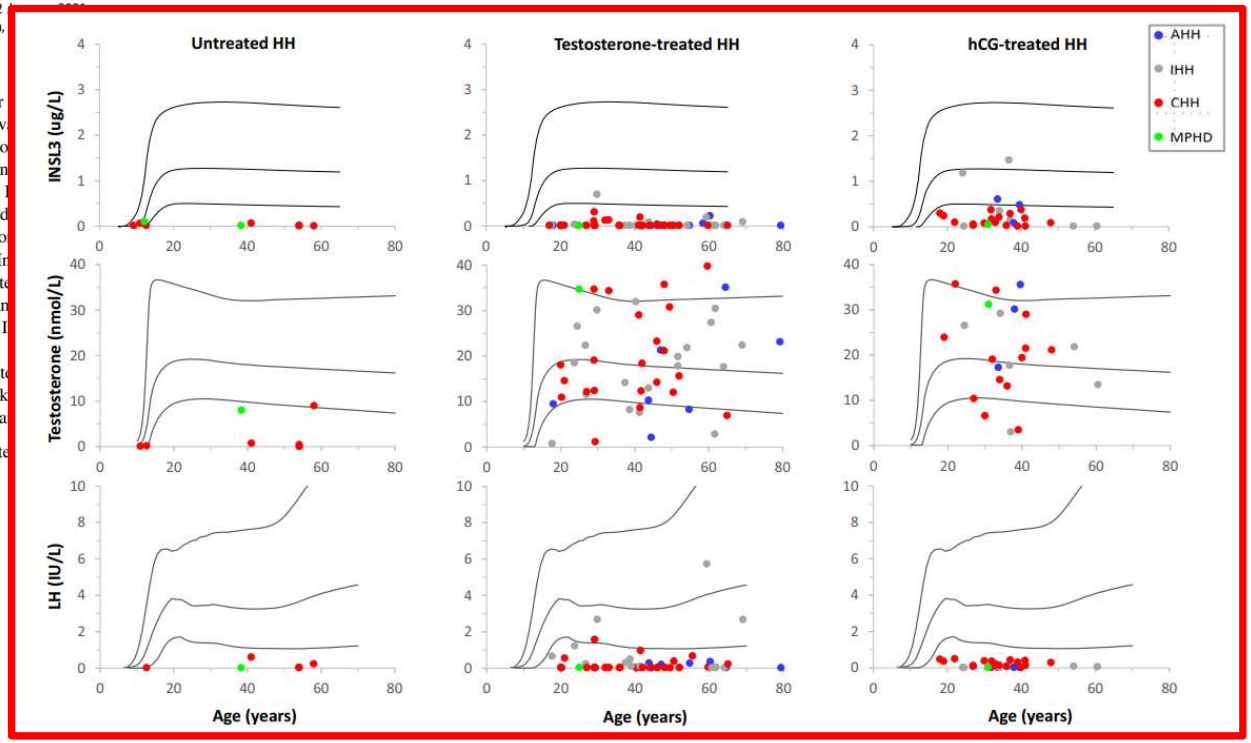
Trine Holm Johannsen[1,2] · Marie Lindhardt Ljubicic[1,2] · Jacques Young[3] · Séverine Trabado[4] · Jørgen Holm Petersen[1,2,5] · Allan Linneberg[6,7] · Jakob Albrethsen[1,2] · Anders Juul[1,2]

Received: 30 October 2020 / Accepted: 5 January 2021 / Published online: 22


**Abstract**

**Purpose** Insulin-like factor 3 (INSL3) is an emerging testicular
INSL3 in patients with hypogonadism are lacking. The aim w
LC–MS/MS methodology in males with hypogonadotropic hypo
**Methods** This was a combined study from two tertiary centers in
LC–MS/MS. In total, 103 patients with HH and 82 patients with
untreated (HH: $n = 7$; KS: $n = 11$). Treatment modalities included
deviation (SD) scores of INSL3, total testosterone, and LH acco
**Results** In both HH and KS, INSL3 concentrations were low. In
some hCG-treated patients with normal concentrations. In untreate
testosterone- and hCG-treated patients. In untreated KS, INSL3 an
testosterone-treated KS, serum INSL3 was low in most patients. I
than in untreated KS ($p = 0.01$).
**Conclusions** The dichotomy between lower INSL3 and higher t
treated patients with HH, confirms that INSL3 is a different mark
clinical application of INSL3 in males with hypogonadism rema

**Keywords** INSL3 · Hypogonadotropic hypogonadism · Klinefelte



# Publications WP5

Endocrine (2022) 75:601–613
https://doi.org/10.1007/s12020-021-02883-y

ORIGINAL ARTICLE

## Pubertal development in 46,XY patients with *NR5A1* mutations

Isabel Mönig[1] · Julia Schneidewind[1] · Trine H. Johannsen[2] · Anders Juul[2] · Ralf Werner[1,3] · Ralf Lünstedt[4] · Wiebke Birnbaum[1] · Louise Marshall[1] · Lutz Wünsch[5] · Olaf Hiort[1]

Received: 18 July 2021 / Accepted: 15 September 2021 / Published online: 6 October 2021


**Abstract**

**Purpose** Mutations in the *NR5A1* gene, encoding the transcription factor Steroidogenic Factor-1, are associated with a highly variable genital phenotype in patients with 46,XY differences of sex development (DSD). Our objective was to analyse the pubertal development in 46,XY patients with *NR5A1* mutations by the evaluation of longitudinal clinical and hormonal data at pubertal age.

**Methods** We retrospectively studied a cohort
features including the external and internal g
FSH, testosterone, AMH, and inhibin B durir

**Results** Patients who first presented in early ir
age accompanied by a significant testosteron
female external genitalia at birth presented la
female puberty. Testosterone levels were high
upper reference range or elevated. Neither the
correlated with the degree of virilization duri

**Conclusion** Patients with *NR5A1* mutations r
puberty. Therefore, it is important to consider

**Keywords** Differences of sex development · N

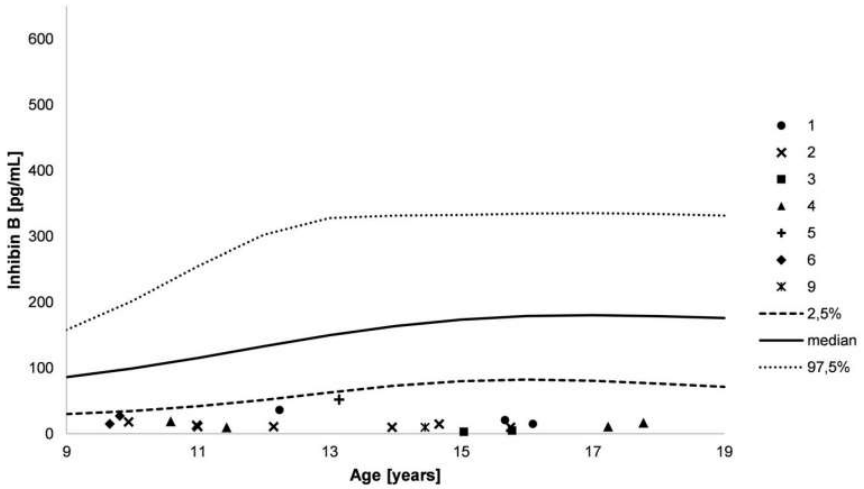



**Fig. 5** Inhibin B levels during course of puberty. Numbers indicate the different patients, lines indicate plus and minus two standard deviations as well as median (male reference data)

# Publications WP5

## Serum Concentrations and Gonada Expression of INSL3 in Eighteen Males With 45,X/46,XY Mosaicism

*Marie Lindhardt Ljubicic [1,2]*, Anne Jørgensen [1,2], Lise Aksglaede [1,2], John Erik Nielser Jakob Albrethsen [1,2], Anders Juul [1,2†] and Trine Holm Johannsen [1,2†]*

*[1] Dept. of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [2] Internationa Center for Research and Research Training in Endocrine Disruption of Male Reproduction and Child Health (EDMaRC Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

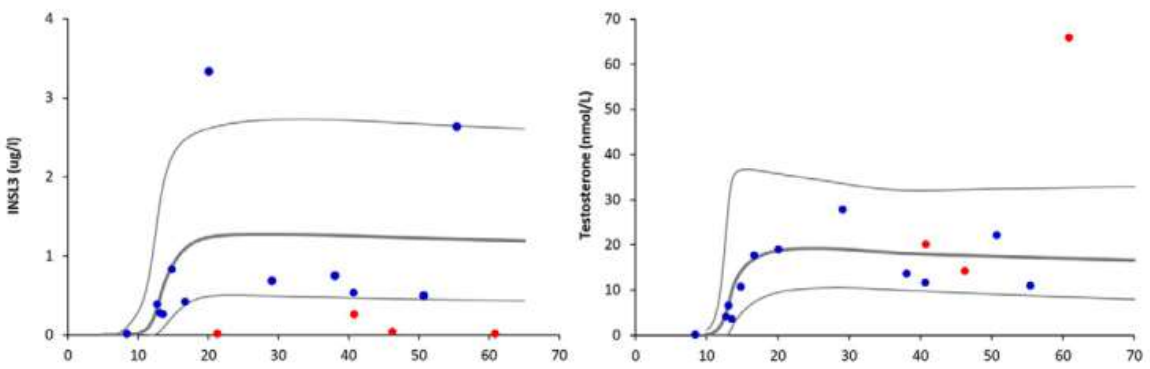
**Objective:** Insulin-like factor 3 (INSL3) is produced in the testes and has been prop as a circulating biomarker of Leydig cell capacity, but remains undescribed in 45,X/ mosaicism. The aim was to examine serum concentrations and gonadal express INSL3 in 45,X/46,XY mosaicism.

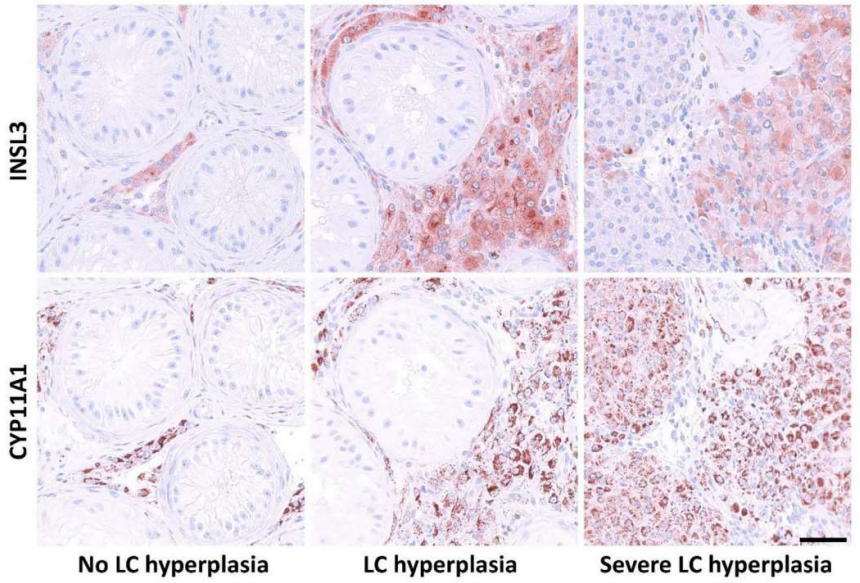
**Methods:** Retrospectively collected data from medical records, gonadal tissue samples, and prospectively analyzed serum samples from eighteen male patients with 45,X/46,XY mosaicism (one prepubertal, four testosterone-treated, 13 untreated) were included. Biochemical, clinical, and histological outcomes were evaluated according to serum INSL3 concentrations, quantified by LC-MS/MS methodology, and gonadal INSL3 immunohistochemical expression.

**Results:** Serum INSL3 concentrations spanned from below to above the reference range. In untreated patients, the median serum INSL3 SD score was -0.80 (IQR: -1.65 to 0.55) and no significant difference was observed between INSL3 and testosterone. There was no clear association between serum INSL3 and External Genitalia Score at diagnosis, spontaneous puberty, or sperm concentration. INSL3 and CYP11A1 expression overlapped, except for less pronounced INSL3 expression in areas with severe Leydig cell hyperplasia. No other apparent links between INSL3 expression and histological outcomes were observed.

**Conclusions:** In this pilot study, serum INSL3 concentrations ranged and seemed independent of other reproductive hormones and clinical features in males with 45,X/46,XY mosaicism. Discordant expression of INSL3 and CYP11A1 may explain low INSL3 and normal testosterone concentrations in some patients. Further studies are needed to elucidate the divergence between serum INSL3 and testosterone and the potential clinical use of INSL3.

**Keywords: INSL3, 45,X/46,XY, LC-MS/MS, gonadal histology, immunohistochemistry**



# Publications WP5

## Serum Concentrations and Gonada Expression of INSL3 in Eighteen Males With 45,X/46,XY Mosaicism

*Marie Lindhardt Ljubicic [1,2*], Anne Jørgensen [1,2], Lise Aksglaede [1,2], John Erik Nielser Jakob Albrethsen [1,2], Anders Juul [1,2†] and Trine Holm Johannsen [1,2†]*

*[1] Dept. of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [2] Internationa Center for Research and Research Training in Endocrine Disruption of Male Reproduction and Child Health (EDMaRC Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

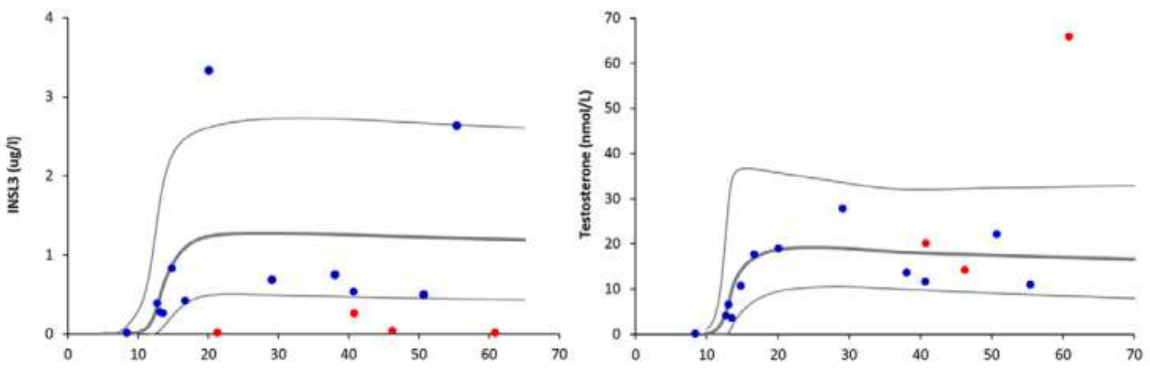
**Objective:** Insulin-like factor 3 (INSL3) is produced in the testes and has been prop as a circulating biomarker of Leydig cell capacity, but remains undescribed in 45,X/ mosaicism. The aim was to examine serum concentrations and gonadal express INSL3 in 45,X/46,XY mosaicism.

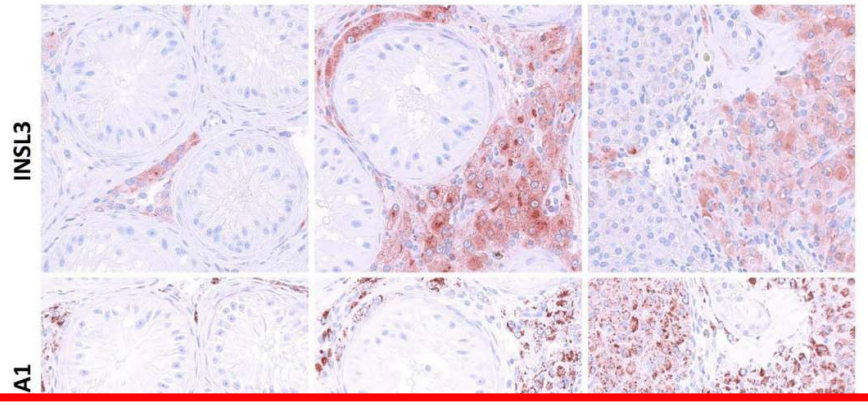
**Methods:** Retrospectively collected data from medical records, gonadal tissue samples, and prospectively analyzed serum samples from eighteen male patients with 45,X/46,XY mosaicism (one prepubertal, four testosterone-treated, 13 untreated) were included. Biochemical, clinical, and histological outcomes were evaluated according to serum INSL3 concentrations, quantified by LC-MS/MS methodology, and gonadal INSL3 immunohistochemical expression.

**Results:** Serum INSL3 concentrations spanned from below to above the reference range. In untreated patients, the median serum INSL3 SD score was -0.80 (IQR: -1.65 to 0.55) and no significant difference was observed between INSL3 and testosterone. There was no clear association between serum INSL3 and External Genitalia Score at diagnosis, spontaneous puberty, or sperm concentration. INSL3 and CYP11A1 expression overlapped, except for less pronounced INSL3 expression in areas with severe Leydig cell hyperplasia. No other apparent links between INSL3 expression and histological outcomes were observed.

**Conclusions:** In this pilot study, serum INSL3 concentrations ranged and seemed independent of other reproductive hormones and clinical features in males with 45,X/ 46,XY mosaicism. Discordant expression of INSL3 and CYP11A1 may explain low INSL3 and nor elucidat use of I

Keywords




## Planned ENDO ERN publication:

**Johannsen TH, Ljubicic ML, Albrethsen A, Neocleous V, Toumba M, Fanis P, Baronio F, Cools M, Juul A.** Evaluation of INSL3 as a marker in DSD: An ENDO-ERN collaborative study

# Outcomes of WP5

**OVERALL OUTCOME**

To promote transnational diagnostics of rare endocrine disorders

**GOALS**

1) Normative sex- and age-related reference ranges uploaded in CPMS
   - Gonadotropins, androgens, 17OHP, growth factors, SHBG, AMH and inhibin B
   - Data is sent to Endo-ERN
   - The CPMS Operational Helpdesk and OpenApp is working on the implementation
     - Expected online in May 2022

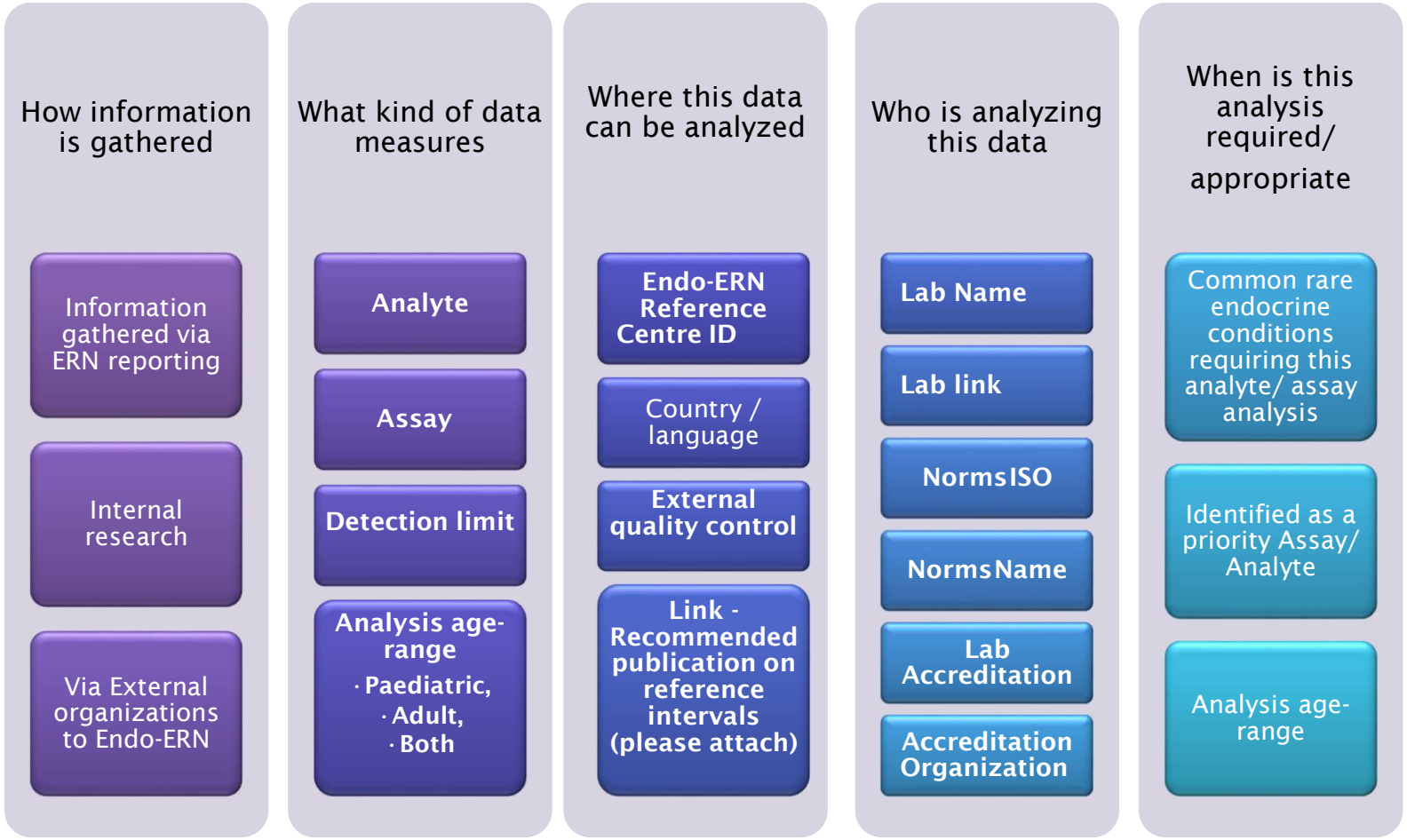
2) A web-based lookup file on where to send samples for specific analyses on the Endo-ERN website
   - Data on diagnostic tests (types, platforms, LODs, quality assessment, publications etc.)
   - 140 analytes
   - Some adjustments are needed before data is ready as a web-based lookup file
     - Emily will present this topic ☺

| A | B | C | I | J |
|---|---|---|---|---|
| Analyte | Assay | Detection limit | External quality control | Link - Recommended publication on ref |
| Chromogranin A | RIA | 1.5 ng/mL | - | |
| Free calcium | Potentiométrie direc | 0,2 mmol/L | ASQUALAB | INTERNATIONAL CONSENSUS |
| Calcitonin (serum) (Cl | DiaSorin Liaison | 1.0 ng/L | UKNEQAS Edinburgh peptide scheme | male<11.8ng/L female<4.8ng/L |
| TSHR-ab | EliA, rTSH | 1.5 UI/L | Biologie prospective | NOTICE MANUFACTURER |

- Sample of the information this database contains
- Missing data needs to be obtained from HCPS, both new and existing members
- Additions to the database fields are based on the following plan

| K | L | M | N | O | P | Q | R | |
|---|---|---|---|---|---|---|---|---|
| Lab Accredation | Lab Name | Lab link | Norms | ISO No | Name | Analysis age-rang | Paediatric, Adult, Both | Co |
| yes | Semmelweis University, Department of Laboratory Medicine, http://semmelwe | | https://www.iso.org/standard | | | yes | both | - |
| | BIOCHEMISTRY | | | | | | | AC |
| Yes | Clinical Biochemistry Department (CX8#12) Charing Cross HospitalFulham P | | 8673UKAS Accredited toISO 15 | | | Yes | Paediatric | |
| YES | Immunochemistry and autoimmunity | | COFRAC | | | Yes | both | AC |

# Assay & Analyte web-based lookup file



# Future Projects

**Important for second term of Endo-ERN:**

We need more input from various stakeholders in these endeavors, particularly biochemical experts, relevant experts in our MTGs and accreditation awarding institutions e.g. ISO.

*Goals to be integrated into new Work Package:*

- Continued development of the Analyte & Assay  we look up program
- Development of lab accreditation quality check
- Review of the “Normative sex- and age-related reference ranges” in CPMS following implementation of this in May 2022

**PLANNED PUBLICATIONS**

- **Mastorakos G, Johannsen TH, Juul A, Memi E, Alexandraki K, Violetis O.** Hypogonadotropic hypogonadism – a new mutation and a review on the existing literature.
- **Johannsen TH, Ljubicic ML, Albrethsen A, Neocleous V, Toumba M, Fanis P, Baronio F, Cools M, Juul A.** Evaluation of INSL3 as a marker in DSD

# Coffee / Tea Break

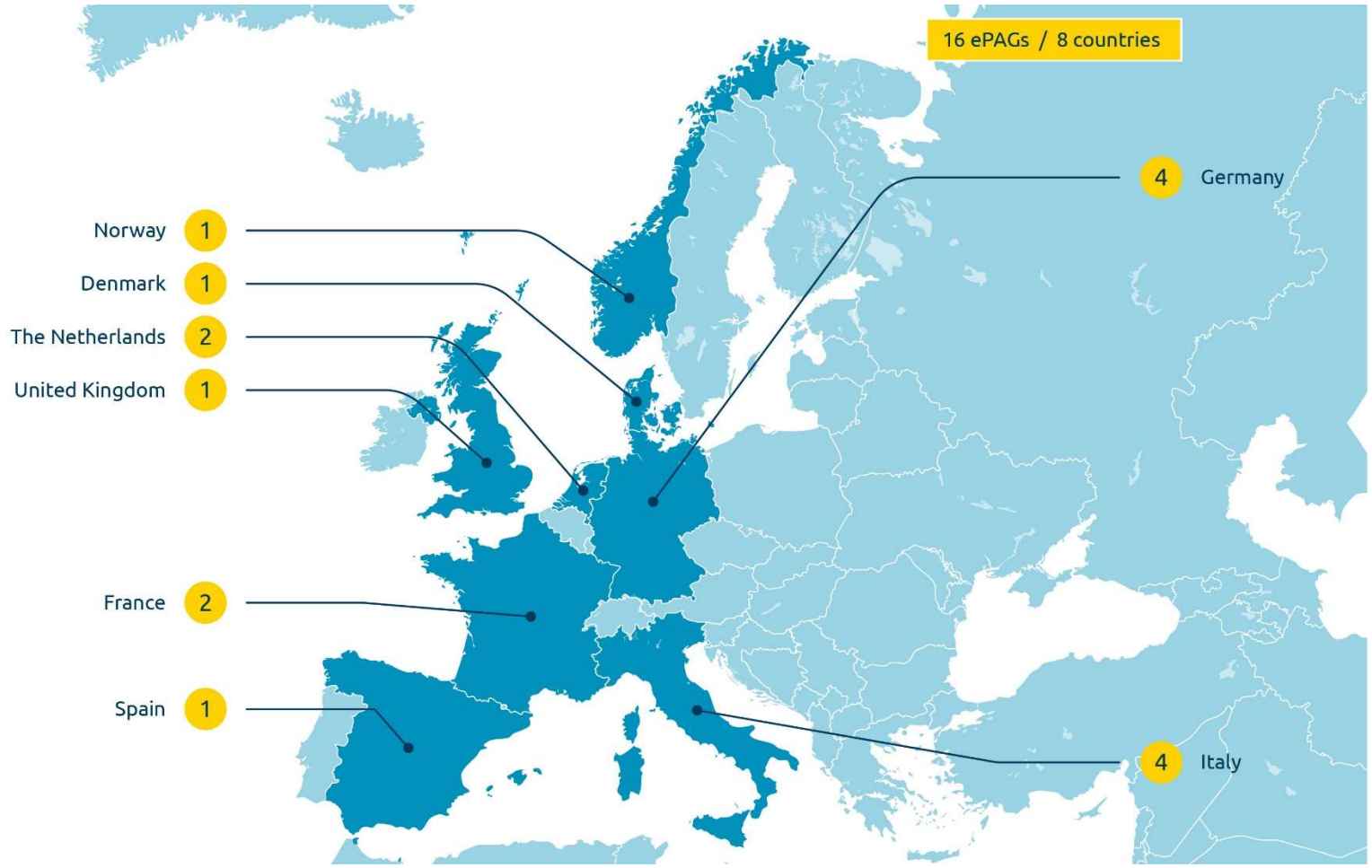
# Until 10:50hrs

# Update from the continuously evolving Endo-ERN ePAGs

# Endo-ERN Patient Representatives

The patient view and voice are implemented at the core of Endo-ERN activities. European Patient Advocacy Group Patient Representatives (ePAGs) are represented in all Main Thematic Groups and preferably also within the different Work-Packages that have been devised to tackle the different goals within Endo-ERN. It is our aim for our patient representatives to represent the different member states within Endo-ERN.

European Patient Advocacy Group


16 ePAGs / 8 countries
Norway 1
Denmark 1
The Netherlands 2
United Kingdom 1
France 2
Spain 1
4 Germany
4 Italy

# Arlene Smyth

- Executive Officer of Turner Syndrome Support Society [UK]
- E-mail:- Turner.syndrome@tss.org.uk https://tss.org.uk/
- Mother to an adult daughter with Turner Syndrome [TS] and founding member
- With over 30 years experience and expertise
- President of Turner Syndrome International Group
- Email:TSI2020@tss.org.uk https://tsint.org
- ERN ePAG co-Chair of MTG7
- Sex development and Maturation
- EuRRECa Board member and part of work package 5
- (Patients, parents and ethics) & data access committee
- I-TS data registry board member

- I am proud to be part of The Office for Rare Condition in Glasgow
- Board member & chair of our Patient advisory Group speaking to families and helping, supporting them and raising awareness about Rare Conditions.
- https://officeforrareconditions.org

# ADDISON FORENINGEN I DANMARK

**National Organization**

*Jette Kristensen, Chair (since 2007)*

Board of 6 (voluntary/unpaid)

Members: 510

Established: 1995

Website: www.addison.dk

Member of: Endo-ERN, AdrenalNET, Eurordis, Sjældne Diagnoser

Network: European Network of Adrenal Patient Organizations

## Endo-ERN

Patientrepresentative in MTG 1 (Adrenals)

Patientrepresentative in WP4 (Quality of Life and Patient View)

# Nathalie FERARD

55 years old. I work part-time as a trainer in a management school.
I live near Clermont-Ferrand, in the center of France.
3 children : Julie 26, Nicolas 23, and Mathis,15 years old.
Mathis has been supplanted in growth hormone from the age of 5, for a Partial Growth Hormone Deficiency.

I am a regional delegate for the Grandir Association and a member of the board, as a volunteer.

Grandir Association is a member of Eurordis since june 2019
I am Endo ERN ePAG since februar 2020.

We were present at the ECE congress in Lyon (may 2019), with a stand of the Association Grandir among the stands of patient associations.

Endo-ERN

Nathalie.ferard@grandir.asso.f
r
https://www.grandir.asso.fr/

GRANDIR

The Grandir association supports and informs about more than 20 pathologies linked to growth in France.

# Patricia Carl-Innig

- Patient representative from Germany
- Member of MTG 5 Growth & Genetic Obesity Syndromes
- Chairwoman of BKMF e.V. (German federal association for short statured people and their families; founded 1988; 3500 members; 90 different diagnoses in endocrine and sceletal spectrum)
- Co-author of several medical articles and patient informations

## Petra Brügmann, Germany

- MEN 1 patient, 62 years, married, retired
- MTG 4 - Genetic Endocrine Tumour Syndromes
- WP 1 Education & Training

Representing

**Network pituitary and adrenal disorders e.V.**

(Board member)

and

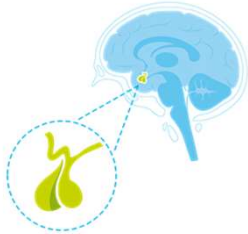
**European MEN Alliance e.V.**

(co-founder, president)

EUROPEAN MULTIPLE ENDOCRINE NEOPLASIA ALLIANCE

# Johan de Graaf, the Netherlands

www.hypofyse.nl



Chair of the Dutch Pitiutary Foundation (founded 1996, 2.200+ members)

ePAG/Steering Committee member MTG 6 Pituitary

ePAG/Steering Committee member WP3 Research and Science

Patient representative EuRRECa WP5 Patients, Parents and Ethics

SEC member EJP-RD (Joint Transnational Calls 2019, 2020, 2021 and probably 2022)

Member review board BMBF funding initiative Translational consortia for rare disease research (2022)

National Expert European Medicines Agency (EMA)

Member of the Patient Expert Board of the Dutch Brain Foundation

Eurordis volunteer

Eupati Fellow

Johan de Graaf – j.degraaf@hypofyse.nl

nederlandse hypofyse stichting

# Diana Vitali

- Endo-ERN ePAG member since 2017
- ePAG Steering Committe MTG6
- ePAG Steering Committee WP4
- Mother of Carolina, with SOD PLUS
- President of SOD ITALIA ONLUS/APS Italian Patient
- Organization for Septo Optic Dysplasia and other Neuroendocrine Disorders.
- Board of ePAG Italia

In normal life Diana works as a sports technician of horse riding and sailing specialized in disabled people.

## Martha Kirchhoff

55 years old. I work in a fulltime job as a nurse in a psychiatric hospital and I am a caregiver to my very old parents.
I live in Germany.
I am mother of two grown up children, one affected with XLH (X linked Hypophosphatemia) and Grandmother 1,5 year old girl.

Patient representative for rare phosphate loss diseases:

- Chair and founding member of the German patient organization for phosphate loss syndromes. (Phosphatdiabetes e.V.) The German patient organization covers members out of Germany, Austria, Swiss and Luxemburg.
- German representative in the International XLH Alliance
- Accredited in the Federal Joint Committee
- ePAG in the ENDO ERN – MTG 2 (disorders of calcium and phosphate homeostasis)

www.Phosphatdiabetes.de
info@phosphatdiabetes.de

PHOSPHATDIABETES E.V.
NETZWERK INFORMATION AUSTAUSCH

Endo-ERN
European Reference Network on Rare Endocrine Conditions

**Beate Bartès**
**Vivre sans Thyroïde, France**
**ePAG Endo-ERN, MTG8 "Thyroid"**

Founder of a discussion forum for thyroid patients in 2000, after being diagnosed with thyroid cancer. President of the non-profit organization "Vivre sans Thyroïde" created in 2007.

Main aim: provide understandable information on thyroid disease, exchange of experience between fellow patients, emotional support. Raise awareness. Patient advocacy.

Website with > 22.000 registered users. 4000-5000 visitors & approx. 100 messages per day. Patient meetings, patient conferences, participation in national and international meetings and congresses (French Endocrine Society, European Thyroid Association…).

Cooperations: France: Alliance for Rare Diseases, Firendo (network for rare endocrine diseases), steering committee of the TuThyRef network for refractory thyroid tumors. International: Thyroid Federation International, Thyroid Cancer Alliance, European Cancer Patient Coalition, Endo-ERN, Eurordis.

www.forum-thyroide.net
info@forum-thyroide.net

**DUTCH ADRENAL SOCIETY NVACP** (founded 1988/1700 members)

- Represented in ENDO-ERN by Johan G. BEUN (till summer ‘22)
- Diana Kwast will be my successor in MTG1
- Johan is one of the founders & former chairman of the NVACP

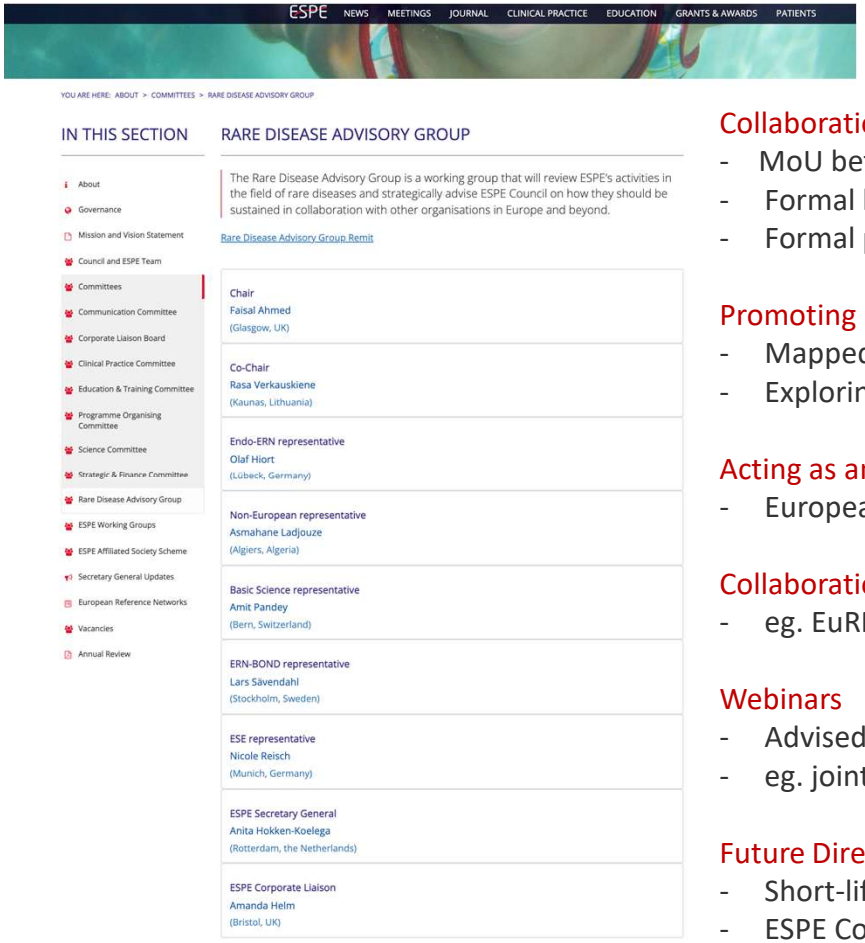
- Johan in daily life is the manager of **AdrenalNET**
- Thank you for yr attention, lots of success ENDO-ERN
- Contact? Johan@Beun.NL

Bijnier vereniging nvacp

# Alignment with ESE / ESPE

**Nicole Reisch & Faisal Ahmed**

https://www.eurospe.org/about/committees/rare-disease-advisory-group/




ESPE
European Society for Paediatric Endocrinology

## Collaboration with ERNs & ESE

- MoU between ESPE, ESE and Endo-ERN
- Formal link with the ESE RD Committee
- Formal process for linking with ERNs including Endo-ERN and ERN-BOND

## Promoting rare disease research

- Mapped ESPE's existing grants and awards that relate to rare disease research
- Exploring projects that support paediatric endocrinologists in research and care

## Acting as an advocate for rare diseases

- European Health Data Space

## Collaboration with rare disease registry projects

- eg. EuRRECa, EuRR-Bone, I-DSD/I-CAH/I-TS, GloBE-Reg

## Webinars

- Advised ESPE Council on rare disease webinars
- eg. joint POC for RD webinars with ESPE, ESE and Endo-ERN representation

## Future Direction

- Short-life advisory group 2021 to 2023
- ESPE Council currently considering options for the longer term

# Round Up

# Lunch Break

# Meet and interact with your MTG co-workers

| | |
|---|---|
| 12:30 – 13:00 | MTG5 Growth & Genetic Obesity Syndromes |
| 13:10 – 13:40 | MTG6 Pituitary |
| 13:50 – 14:20 | MTG7 Sex Development & Maturation |
| 14:30 – 15:00 | MTG8 Thyroid |

# See the handouts for the meeting links