

Dear colleague

We are contacting you in the context of the MTG7 working group “Sexual Development and Maturation” of ENDO-ERN.

This survey is aimed to collect data for the preparation of a manuscript on the “Variable usage across Europe of NGS analyses for the diagnosis and management of patients with DSD, CHH, POI”

We ask questions specifically aimed to understand how the genetic diagnosis of these conditions is currently achieved in our European settings.

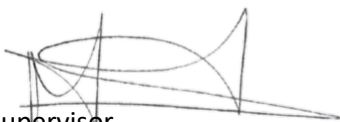
Depending on your local circumstances, it may be needed to forward this survey to a colleague at your institution (e.g. molecular geneticist, bioinformatic), or to complete the survey together with this person.

If you have any further questions or remarks, please contact us.

Looking forward to your response!


Kind regards

Martine Cools



Supervisor

Luca Persani



Supervisor

Olaf Hiort



GENERAL

Center:

Name responsible:

Please, provide contact email of the responsible:

Period during which NGS data were gathered:

1. TARGETED NGS SEQUENCING (Candidate gene panel)

Patients and genes

In the following section, we ask you to provide an overview of the amount of data your center obtained using targeted resequencing of known DSD/CHH genes. In case you don't use a separate panel for both conditions, but have a joint panel, please provide the numbers at the 'combo' field. This field can also be used if your panel also targets other related conditions or subcategories of the main conditions (eg: CAH for 46,XX DSD). If this is the case, please specify these conditions under 'Remarks', including an OMIM or Orphanet code.

1A. Patients

46,XX DSD:

46,XY DSD:

CHH:

46,XX POI <25 years:

1B. Number of included genes

46,XX DSD:

46,XY DSD:

CHH:

46,XX POI <25 years:

Combo:

1C. Please, provide the number of cases with at least one likely pathogenic variant (ACMG Class IV or V variant or otherwise specified, in the heterozygous or homozygous state) or with an oligogenic involvement:

46,XX DSD:

46,XY DSD:

CHH:

46,XX POI <25 years:

Technical details

In this section we will ask you to give us some more information on how the data is generated and analyzed in your center. Please provide the information chronologically and as detailed as possible.

1D. These targeted NGS analyses are performed for:

- diagnostics reasons (reimbursed by the National Health System): YES/NO
- otherwise supported by the NHS: YES/NO
- supported by other resources: YES/NO
- research: YES/NO

1E. Panel used:

- In-house commercial: Yes/No
- In-house custom: Yes/No
- Outsource service: Yes/No

1F. Bioinformatics:

Contact information of the responsible bioinformatician or computational biologist for the study:

1G. Confirmation: are the identified variants confirmed using a second sequencing technique, if so which one?

1H. In your report, do you include:

- Pathogenic variants only: YES/NO
- Rare non-synonymous variants of unknown significance (VUS with MAF <0.01): YES/NO

- Synonymous variants: YES/NO
- All intronic variants: YES/NO
- Unattended results in non-disease related genes: YES/NO
- How do you define pathogenic variants?

11. Do you follow one of the following guidelines for the definition of variants? Please indicate which one:

- Richards S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine* 2015 17 405–424. (<https://doi.org/10.1038/gim.2015.30>)
- Matthijs G, et al. Guidelines for diagnostic next-generation sequencing. *European Journal of Human Genetics* 2016 24 2–5. (<https://doi.org/10.1038/ejhg.2015.226>)
- Roy S, et al. Standards and guidelines for validating next-generation sequencing bioinformatics pipelines: a joint recommendation of the association for Molecular Pathology and the College of American Pathologists. *Journal of Molecular Diagnostics* 2018 20 4–27. (<https://doi.org/10.1016/j.jmoldx.2017.11.003>)
- Other?, please specify

Remarks:

2. WHOLE EXOME or GENOME SEQUENCING (WES or WGS)

Patients

2A. Patients (Please specify the number of WES or WGS)

46,XX DSD:

46,XY DSD

CHH:

46,XX POI <25 years:

Other related conditions:

2B. Please, specify the included conditions (provide OMIM number and number of patients for each) and indicate the fraction of total patients that you run on WES or WGS under 'Remarks'

Remarks:

2C. Are WES/WGS always run in trios: YES/NO

2D. These WES/WGS analyses are performed for:

- diagnostics reasons (reimbursed by the NHS): YES/NO
- otherwise supported by the NHS: YES/NO
- supported by other resources: YES/NO
- research: YES/NO

Technical details

In this section we will ask you to give us some more information on how the data is generated and analyzed in your center. Please provide the information chronologically and as detailed as possible.

2E. Platform used:

- In-house: Yes/No
- Outsource service: Yes/No

2F. Sample preparation: enrichment, fragmentation, adaptor ligation, ...

2G. Sequencing: sequencer, etc ...

2H. Bioinformatics:

Contact information of the responsible bioinformatician or computational biologist for the study:

2I. Confirmation: are the identified variants confirmed using a second sequencing technique, if so which one?

Remarks:

2J. In your report, do you include:

- Pathogenic variants only: YES/NO
- Rare non-synonymous variants of unknown significance (VUS with MAF <0.01): YES/NO
- Synonymous variants: YES/NO
- All intronic variants: YES/NO
- Do you include unattended results in non-disease related genes: YES/NO
- How do you define pathogenic variants?

2K. Do you define variants following guidelines? YES/NO

If Yes, please indicate which one:

- Richards S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the

Association for Molecular Pathology. Genetics in Medicine 2015 17 405–424.
(<https://doi.org/10.1038/gim.2015.30>)

- Matthijs G, et al. Guidelines for diagnostic next-generation sequencing. European Journal of Human Genetics 2016 24 2–5. (<https://doi.org/10.1038/ejhg.2015.226>)
- Roy S, et al. Standards and guidelines for validating next-generation sequencing bioinformatics pipelines: a joint recommendation of the association for Molecular Pathology and the College of American Pathologists. Journal of Molecular Diagnostics 2018 20 4–27.
(<https://doi.org/10.1016/j.jmoldx.2017.11.003>)
- Other?, please specify

3. IMPACT OF NGS ANALYSES ON CLINICAL MANAGEMENT

How was the management of patients and their families changed after the NGS analyses?

- Improved with a more precise management of the patient: YES/NO

If YES, please provide some more information/examples:

- Improved management of the family: YES/NO

If YES, please provide some more information/examples:

- Unchanged management of the patient: YES/NO

If YES, please provide some more information:
