



## **ECFS – Diagnostic Network Working Group (DNWG)**

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DNWG-assistant: Marlies Destoop

### **Annual report, May 2020**

#### **Aims**

The European CF Society Diagnostic Network Working Group (ECFS DNWG) was set up to evaluate new diagnostic techniques and to standardize procedures throughout Europe. The goal of this Network is to achieve pan-European cooperation on the definitions of disease, standardization of electrophysiological and genetic techniques and the exchange of information, discussion of difficult cases and the development of new diagnostic technologies. Diagnostic techniques are also used as biomarkers in clinical trials for CF, which has led to a cooperation between the DNWG and the ECFS-CTN and the CFF TDN. A close cooperation with the newborn screening working group (ECFS NSWG) and the European CF-Registry remains also an important goal of the ECFS DNWG.

#### **Membership**

All members of the ECFS with an interest in diagnostic topics in CF are welcome to participate in the work of ECFS DNWG. In June 2019 (handover of the coordinator), the group had 109 members from 49 different countries. Fifty-four (49%) of those members were not official ECFS members in 2019, which is unacceptable. Therefore, we strongly advised active participation in the working group was contingent on ECFS membership. DNWG-members who have not participated in 4 subsequent annual meetings (n=29) were addressed by e-mail, and asked if they still wanted to be members of DNWG and reminded of the need to be an ECFS member, highlighting again the goals of the working group and the inclusion criteria (official ECFS-member). An updated list will be provided soon to the ECFS-board.

#### **Meetings**

The ECFS DNWG meets at least twice a year usually at the ECFS conference and at a separate weekend during the year (annual DNWG-meeting in February).

During the last 12 months the DNWG group had the following meetings

- Meeting at the annual ECFC: Liverpool (open meeting)  
This meeting mainly focused on the handover of the coordinator. Timelines were highlighted, as well as ongoing and future projects. Three oral poster presentations regarding diagnosis were incorporated in the program.

- Meeting at the annual NACFC: Nashville (closed meeting)  
The following topics were discussed in order to proceed with ongoing projects. Sweat test: how to move forward? NPD: standardisation study and NPD solutions. ICM: standardisation study. DNWG-website. Preparation of the Utrecht meeting. (Report of the meeting is attached)
- 17<sup>th</sup> Annual DNWG-meeting in Utrecht, The Netherlands 6<sup>th</sup>-8<sup>th</sup> February 2020, hosted by Inez Bronsveld. Sixty-five people attended this meeting. (Program and report of the meeting is attached)

#### Next meetings:

- Due to the COVID-19 situation, ECFC cannot take place in Lyon as foreseen. People within the DNWG-group were in the previous weeks/months actively involved in the health care for patients infected with Coronavirus. This resulted in a delay in the organisation of a complete program from the DNWG for the Annual ECFC meeting. However, we plan an online meeting at the end of the summer, informing DNWG-members about ongoing projects and inviting speakers to present their work within the diagnostic field.
- We plan to organize again an annual closed meeting at NACFC. The format of this meeting will depend on the development in the COVID-19 situation (Web-based or real life)
- 18<sup>th</sup> Annual ECFS DNWG meeting February 2021 is in preparation.

### Young investigators

We are actively promoting the involvement of Young Investigators to the DNWG group activities, including oral presentations/Young Investigator Travel Awards at the Annual group meetings. Within

the Utrecht meeting in 2020, we included presentations of 4 Young Investigators (who received a travel grant) from Germany, Russia, Turkey, and Poland. For more details, please see the attached report of the Annual meeting.



ECFS DNWG Young Investigators 2020

(left to right: Nick Simmonds, Inez Bronsveld, Zeynep Reyhan Onay, Yulia Melyanovskaya, Magdalena Postek, Simon Gräber, Elke De Wachter)

## Website

The DNWG website ([http://www.ecfs.eu/ecfs\\_dnwg](http://www.ecfs.eu/ecfs_dnwg)) is located within the ECFS website. It has been slightly updated and advertised at different conferences and in communication with partners. Regular news, meeting programs, publications and contact details are shown. People can contact the core group of DNWG by sending an e-mail to [dnwg@ecfs.eu](mailto:dnwg@ecfs.eu), avoiding no response if the request is addressed to one person.

## Ongoing projects and future plans

### 1. Sweat test

- Training sessions (sweat test hands on)
- DNWG position paper
- Step-wise sweat test protocol (SOP) on the ECFS website after finalizing the position paper

### **Improving sweat test performance in Europe: development of new ECFS DNWG training resources:**

From a European ECFS DNWG sweat test survey we have learned about important deficiencies/barriers in routine sweat testing in real life in Europe (Cirilli N et al. JCF 2017).

The ECFS DNWG therefore has previously organized several Hands-on Training Workshops to improve practical sweat test performance in Europe. The last ECFS DNWG Sweat test Training Workshop „Practical aspects for improvement of CF diagnosis in Europe“ was held at ECFC Liverpool 2019. Due to conflict of dates in 2020 this workshop did not have place at the Middle-East CF conference this year. Unfortunately, due to the COVID pandemic, the planned session (Wed, 3<sup>rd</sup> June) will not take place in Lyon. These Hands-on Training Workshops use the most updated current international guidelines and the ECFS CTN sweat test SOP, using the Wescor Macroduct system.

Presently, we believe that more people can be involved in sweat test training by improving the currently available information on the ECFS DNWG-website. Along the filmed session of last year's Hands-on Training we are planning to publish a step-wise Sweat test protocol (DNWG-SOP), illustrated with pictures of each step and a Q&A document available on the DNWG website. As a group, we agree that information on sweat test performance without the expensive equipment of Wescor, referring to the older Gibson and Cook method, should be available on the ECFS DNWG website, as this fits into the ECFS strategy to support also low-income countries. Before we can achieve this, the sweat test working group is in charge of writing a new position paper on how to perform a sweat test for diagnosing CF in Europe and beyond. A first draft has been made. After publication, the DNWG website should be adapted in line with the recommendations of the working group.

*Project Core group: Natalia Cirilli, Elke De Wachter, Nick Simmonds.*

*Project working group: Natalia Cirilli, Kevin W Southern, J. Barben, F. Vermeulen, A. Munck, M. Wilschanski, Merica Aralica, Nico Derichs, N. Simmonds, E. De Wachter.*

Some people involved in the core group are in charge of running educational programs aiming to improve sweat test performance. South Eastern CF conference, Educational project in Morocco...

## 2. CFTR biomarkers: standardization and diagnostic reference values

The "standard" test for diagnosing CF is the sweat test. However, an increasing group of patients cannot be diagnosed with the sweat test as results are in an intermediate range of CFTR dysfunction. Alternative tests have been developed to ascertain and further quantify the basic defect in CF, the lack of CFTR-mediated chloride ion transport. The nasal potential difference (NPD) test examines the chloride transport in the nose and the intestinal current measurement (ICM) examines CFTR function ex vivo in rectal biopsies. Both these tests have been further optimised in recent years, and new European SOPs have been developed by the ECFS DNWG for use as a diagnostic aid and for therapeutic outcome strategies in Europe. These SOPs for ICM and NPD will allow inter-centre comparison of results and reference values. The last step in the process is the finalization of the manuscripts of the validation studies for NPD and ICM. Authors will be contacted again to progress this and agree completion timelines.

*NPD core group: Inez Bronsveld, Isabelle Sermet, Michael Wilschanski*

*ICM core group: H De Jonge, Nico Derichs, Lutz Nährlich*

## 3. Development of new guidelines on CFTR-related disorders (CFTR-RD)

CFTR-RD is a clinical entity associated with variable levels of CFTR-dysfunction, that does not fulfil the diagnostic criteria for CF. The Bombieri paper (JCF Bombieri 2011) discussed the utility of sweat testing, mutation analysis, nasal potential difference, and/or intestinal current measurement for the differential diagnosis of CF and CFTR-RD. Entities considered as CFTR-RD in this manuscript are CBAVD, acute recurrent or chronic pancreatitis and disseminated bronchiectasis with CFTR dysfunction. This paper dates from about 10 years ago. Meanwhile, new insights have been made (for example: the 2011 paper does not refer to CFTR2).

The DNWG has decided to write new guidelines on CFTR-RD, not only focusing on differential diagnosis, but also on definition, care, treatment and long-term evolution.

This project started in March 2020. Timelines are extended due to the COVID-19 situation.

*CFTR-RD core group: Carlo Castellani, Kevin W Southern, Elke De Wachter, Nick Simmonds, Kris De Boeck*

In the scope of this task 2 small projects, using an online questionnaire, have been set up together with young investigators (students):

- Do fertility clinics use the current recommendations to exclude CF in CBAVD men? A pilot study (*Marlies Destoop, Elke De Wachter*)
- How to diagnose difficult cases: is it CF, CFTR-RD or CFSPID? (*Carlo Castellani and student*)

## 4. Upcoming projects that receive the support from DNWG:

- **Diagnosing cystic fibrosis in Belgian patients: novel methods and multimodal platform**

François Vermeulen (UZLeuven, B) is PI of this study. The aim of this study is to use the organoid model as a diagnostic tool for CF diagnosis.

- **MucoSWEATomics: Proteome, peptidome and metabolome of sweat and the sweat gland: a search for new biomarkers for CF.**

Teresinha Leal and Audrey Reynaerts are PI of this study. In contrast to previous studies the goals of this project is to investigate the sweat gland itself. Skin biopsies are performed in order to examine the sweat gland and its metabolites, proteome and peptidome with the use of mass-spectrometry. Results will be compared between CF patients, carriers and healthy volunteers in order to find out if a

significant difference in the behaviour of the sweat test can be seen, and could be indicated as a new biomarker for CFTR-dysfunction. Secondly, this study will investigate if the results of the biopsy can be extrapolated to the findings of mass-spectrometry in sweat, obtained by pilocarpine iontophoresis, making the analysis less invasive.

## Publications 2019-2020

Aalbers BL, Yaakov Y, Derichs N, Simmonds NJ, De Wachter E, Melotti P, De Boeck K, Leal T, Tümmler B, Wilschanski M, Bronsveld I. Nasal potential difference in suspected cystic fibrosis patients with 5T polymorphism. *J Cyst Fibros*. 2019 Jul 19. pii: S1569-1993(19)30822-7. doi: 10.1016/j.jcf.2019.07.001. PubMed PMID: 31331863.

Kyrilli S, Henry T, Wilschanski M, Fajac I, Davies JC, Jais JP, Sermet-Gaudelus I. Insights into the variability of nasal potential difference, a biomarker of CFTR activity. *J Cyst Fibros*. 2019 Nov 4. pii: S1569-1993(19)30899-9. doi: 10.1016/j.jcf.2019.09.015. [Epub ahead of print] PubMed PMID: 31699569.

Morris-Rosendahl DJ, Edwards M, McDonnell MJ, John S, Alton EW, Davies JC, Simmonds NJ. Whole Gene Sequencing of CFTR Reveals a High Prevalence of the Intronic Variant c.3874-4522A>G in Cystic Fibrosis. *Am J Respir Crit Care Med*. 2020 Feb 4. doi: 10.1164/rccm.201908-1541LE. [Epub ahead of print] PubMed PMID: 32017858.

## Publications on newborn screening 2019-2020

Chudleigh J, Ren CL, Barben J, Southern KW. International approaches for delivery of positive newborn bloodspot screening results for CF. *J Cyst Fibros*. 2019 Sep;18(5):614-621. doi: 10.1016/j.jcf.2019.04.004. Epub 2019 Apr 30. PubMed PMID: 31047829.

Southern KW, Barben J, Gartner S, Munck A, Castellani C, Mayell SJ, Davies JC, Winters V, Murphy J, Salinas D, McColley SA, Ren CL, Farrell PM. Inconclusive diagnosis after a positive newborn bloodspot screening result for cystic fibrosis; clarification of the harmonised international definition. *J Cyst Fibros*. 2019 Nov;18(6):778-780. doi: 10.1016/j.jcf.2019.04.010. Epub 2019 Apr 24. PubMed PMID: 31027826.

11<sup>th</sup> May 2020



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