ECFS – Diagnostic Network Working Group (DNWG)

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Annual report, May 2019

Introduction & Aims:

The European CF Society Diagnostic Network Working Group (ECFS DNWG) was set up in 2003 to develop consensus on CF diagnosis definitions and terminology, to evaluate and standardize new diagnostic techniques and to improve the diagnosis of CF throughout Europe by international cooperation and networking. The goals of the ECFS DNWG are also closely related to precise documentation of CF diagnosis in patient registries and application of diagnostic techniques for drug development and clinical trials in CF, in cooperation with the ECFS Patient Registry and the ECFS Clinical Trials Network.

Membership:

All members of the ECFS with an interest in diagnostic topics in CF (except companies) are welcome to participate in the scientific work of ECFS DNWG. Presently, the group has 104 members from 53 countries (Figure 1). In 2012 there have been 55 members from 18 countries.

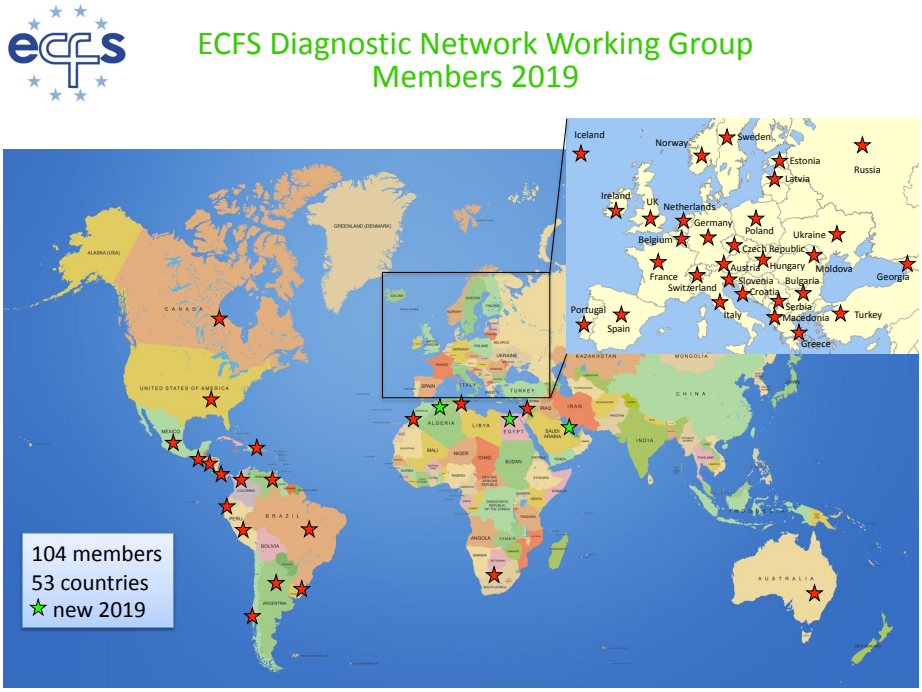

Figure 1. Overview of members (2019) within the ECFS Diagnostic Network Working Group.

Meetings:

The ECFS DNWG meets at least twice a year usually at the ECFS conference and at a separate weekend during the year.

During the last 12 months, the group had several meetings to discuss work progress and present results to interested participants:

- Meeting at ECFC 2018 in Belgrade (open to all conference participants)
- 16th Annual Group Meeting in Tunis, Tunisia 14th – 16th February 2019 (see program and detailed meeting report on the website)

Special activities 2018/2019:

- **Organisation of 3 ECFS DNWG Sweat test Training Workshops „Practical aspects for improvement of CF diagnosis in Europe“ at:**
  - ECFC Belgrade 2018
  - Middle East CF Conference Istanbul 2019
  - ECFC Liverpool 2019

Regular networking activities include:

- Involvement of new countries, new members, encouraging ECFS membership
- Call for CF diagnostic cases at ECFC Conference DNWG meeting (since 2013): Regular involvement of new local CF caregivers to DNWG
- Collaboration with CFF, ECFS Education Project, ECFS Neonatal Screening Working Group, ECFS Patient Registry, ECFS Clinical Trials Network, CF Europe, National Organisations

Next meetings:

- DNWG Meeting at ECFC in Liverpool, Friday 7th June 2018, 12:30 to 14:30 (open to all conference participants)
- 17th Annual ECFS DNWG meeting, February 2020 (in preparation)

Young Investigators:

We are actively promoting the involvement of Young Investigators to the DNWG group activities and oral presentations/Young Investigator Travel Awards at the Annual group meetings. Within the Tunis meeting in 2019, we included presentations of 5 Young Investigators from Czech Republic, Belgium, Poland and Italy. Details can be seen in the Meeting report on the website.

Website:

The DNWG website (http://www.ecfs.eu/ecfs_dnwg), located within the ECFS website, is regularly updated and advertised at different conferences and in communication with partners. Regular news, projects, meeting programs, publications and contact details are communicated.

News, Activities, Projects:

Improving sweat test performance in Europe: development of new ECFS DNWG training resources (N. Cirilli, K. Southern, N. Derichs)

From an European ECFS DNWG sweat test survey we have learned about important deficiencies in sweat test routine in real life in Europe (Ciriili N et al. JCF 2017).
The ECFS DNWG therefore is organizing several Hands-on Training Workshops to improve practical sweat test performance in Europe:

ECFS DNWG Sweat test Training Workshop „Practical aspects for improvement of CF diagnosis in Europe“ at ECFC Belgrade 2018, Middle East CF Conference 2019 and ECFC Liverpool 2019.
This hands-on workshop for sweat test procedure is describing the current international guidelines and the ECFS CTN sweat test SOP and will provide original hands-on testing including important details for quality assurance. Participants come from across Europe, with a focus on Eastern European countries.

Real life practice of sweat testing in Europe and development of an ECFS sweat test guideline for diagnosis of CF (N. Cirilli, N. Derichs)

Project Core Group: Natalia Cirilli, Kevin Southern, Jürg Barben, Lutz Nährlich, Anne Munck, Michael Wilschanski, Kris De Boeck, Nico Derichs

This project started by performing a survey about the current sweat test practice in Europe. The aim of the project was to better understand and improve sweat test practices in European countries, and to develop harmonised European recommendations on sweat testing in real life settings.
Main Objectives:
1) to assess current sweat test practice across Europe
2) to identify examples of good practice and challenges
3) to develop and agree minimal sweat test standards
4) to form a European consensus on recommendations for good real life practice
5) to develop training resources to support sweat testing services across Europe
Results of this project were presented at ECFC Basel 2016 and at the ECFS DNWG Meeting in Ljubljana 2017. Final results have been published in the Journal of Cystic Fibrosis in Sept 2017.

CFTR biomarker: standardisation and diagnostic reference values (I. Sermet, I. Bronsveld, M. Wilschanski, H. De Jonge, N. Derichs)

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. Therefore, also newer 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, 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 centre-independent comparison of results and reference values. In the last WG period, we extensively worked together on a multicenter basis to validate the new SOPs. Results of this project were presented at ECFC Basel (Workshop 18) and at the ECFS DNWG Meeting in Ljubljana 2017. Presently, we are preparing ECFS DNWG Position Papers on this topic.

Complete CFTR gene mutation analysis in European patients with Cystic Fibrosis (H. Cuppens, K. De Boeck)

Aim: to provide a service for highly parallel sequencing of the complete CFTR gene (including intronic and promoter regions) in patients with confirmed CF in whom a disease-causing mutation was not found on both CFTR genes.
Criteria for inclusion:

- the local CF physician confirms the diagnosis of 'classic' CF according to the European CF diagnostic criteria (Thorax 2006): patient has symptoms compatible with CF OR a sibling with CF OR a positive test at newborn screening AND a sweat chloride value >60 mmol/L.
- routine CFTR mutation screening panels have not allowed identification of 2 CF-causing CFTR mutations.
- a signed written informed consent, according to the institute's ethical committee regulations and approvals, is signed by the patient and the local physician and archived locally. This consent must include that the mutation information and the clinical data of the patient will be listed anonymously in a central archive and that the results of the entire project will be published in a scientific journal.
- patient does not reside in UK, Spain or Czech Republic (separate program is available).
- 2 to 5 microgram of DNA is available.

First results of this project were presented at the ECFS DNWG Meeting in Ljubljana 2017.

Publications:

The ECFS DNWG has published an algorithm on the diagnosis of CF and subsequently validated it multicentrally across Europe:
De Boeck K, Wilschanski M, Castellani C, Taylor C, Cuppens H, Dodge J, Sinaasappel M; Diagnostic Working Group. Cystic fibrosis: terminology and diagnostic algorithms. Thorax 2006;61(7):627-35.

Goubau C, Wilschanski M, Skalicka V, Lebecque P, Southern K, Sermet I, Munck A, Derichs N, Middleton P, Hjelte L, Padoan R, Vasar M, De Boeck K. Phenotypic characterization of patients with intermediate sweat chloride values: towards validation of the European diagnostic algorithm for cystic fibrosis. Thorax 2009; 64(8):683-91.

Also, several publications on specific diagnostic aspects in CF have been published by the ECFS DNWG and its members (selection):

Cirilli N, Southern KW, Buzzetti R, Barben J, Nährlich L, Munck A, Wilschanski M, De Boeck K, Derichs N; on behalf of the ECFS Diagnostic Network Working Group. J Cyst Fibros. 2017 Sep 27. pii: S1569-1993(17)30881-0. doi: 10.1016/j.jcf.2017.09.002.
Munck A, Mayell SJ, Winters V, Shawcross A, Derichs N, Parad R, Barben J, Southern KW. Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID): A new designation and management recommendations for infants with an inconclusive diagnosis following newborn screening. J Cyst Fibros 2015 Jan 24.
Keenan K, Avolio J, Rueckes-Nilges C, Tullis E, Gonska T, Naehrlich L. Nasal potential difference: Best or average result for CFTR function as diagnostic criteria for cystic fibrosis? J Cyst Fibros 2014 Oct 6. pii:S1569-1993(14)00217-3.
Beekman JM, Sermet-Gaudelus I, de Boeck K, Gonska T, Derichs N, Mall MA, Mehta A, Martin U, Drumm M, Amaral MD. CFTR functional measurements in human models for diagnosis, prognosis and personalized therapy: Report on the pre-conference meeting to the 11th ECFS Basic Science Conference, Malta, 26-29 March 2014. J Cyst Fibros 2014 Jul;13(4):363-72.
De Boeck K, Zolin A, Cuppens H, Olesen HV, Viviani L. The relative frequency of CFTR mutation classes in European patients with cystic fibrosis. J Cyst Fibros 2014; 13(4): 403-9.
Thomas M, Lemonnier L, Gulmans V, Naehrlich L, Vermeulen F, Cuppens H, Castellani C, Norek A, De Boeck K. Is there evidence for correct diagnosis in cystic fibrosis registries? J Cyst Fibros 2013 Nov 22 Epub.
Naehrlich L, Ballmann M, Davies J, Derichs N, Gonska T, Hjelte L, van Konigsbruggen-Rietschel S, Leal T, Melotti P, Middleton P, Tümmler B, Vermeulen F, Wilschanski M; on behalf of the ECFS Diagnostic Network Working Group. Nasal potential difference measurements in diagnosis of cystic fibrosis: An international survey. J Cyst Fibros 2014;13(1):24-8.
Derichs N, Pinders-Kessler L, Bronsveld I, Scheinert S, Rückes-Nilges C, de Jonge HR, Naehrlich L. Multicenter European standardization and reference values for intestinal current measurement in rectal biopsies. Pediatr Pulmonol 2013; 48(S36):300.
Bronsveld I, Vermeulen F, Sands D, Leal T, Leonard A, Melotti P, Yaakov Y, de Nooijer R, De Boeck K, Sermet I, Wilschanski M, Middleton PG; European Cystic Fibrosis Society – Diagnostic Network Working Group. Influence of perfusate temperature on nasal potential difference. Eur Respir J 2013; 42(2):389-93.
De Boeck K, Kent L, Davies J, Derichs N, Amaral M, Rowe S, Middleton P, de Jonge H, Bronsveld I, Wilschanski M, Melotti P, Danner-Boucher I, Boerner S, Fajac I, Southern K, de Nooijer R, Bot A, de Rijke Y, de Wachter E, Leal T, Vermeulen F, J Hug M, Rault G, Nguyen-Khoa T, Barreto C, Proesmans M, Sermet-Gaudelus I; On behalf of the European Cystic Fibrosis Society Clinical Trial Network Standardisation Committee. CFTR biomarkers: time for promotion to surrogate endpoint? Eur Respir J 2013; 41(1):203-216.
De Boeck K, Derichs N, Fajac I, de Jonge HR, Bronsveld I, Sermet I, Vermeulen F, Sheppard DN, Cuppens H, Hug M, Melotti P, Middleton PG, Wilschanski M. ECFS Diagnostic Network Working Group. New clinical diagnostic procedures for cystic fibrosis in Europe. J Cyst Fibros 2011; 10

Suppl 2:S53-66.
Bombieri C, Claustres M, De Boeck K, Derichs N, Dodge J, Girodon E, Sermet I, Schwarz M, Tzetis M, Wilschanski M, Bareil C, Bilton D, Castellani C, Cuppens H, Cutting GR, Drevinek P, Farrell P, Elborn JS, Jarvi K, Kerem B, Kerem E, Knowles M, Macek M Jr, Munck A, Radojkovic D, Seia M, Sheppard DN, Southern KW, Stuhrmann M, Tullis E, Zielenski J, Pignatti PF, Ferec C. Recommendations for the classification of diseases as CFTR-related disorders. J Cyst Fibros 2011; 10 Suppl 2:S86-S102.
Derichs N, Sanz J, von Kaenel T, Stolpe C, Zapf A, Tümmler B, Gallati S, Ballmann M. Intestinal current measurement for diagnostic classification of patients with questionable cystic fibrosis: validation and reference data. Thorax 2010; 65(7):594-99.
Sermet-Gaudelus I, Girodon E, Roussel D, Deneuville E, Bui S, Huet F, Guillot M, Aboutaam R, Renouil M, Munck A, des Georges M, Iron A, Thauvin-Robinet C, Fajac I, Lenoir G, Roussey M, Edelman A. Measurement of nasal potential difference in young children with an equivocal sweat test following newborn screening for cystic fibrosis. Thorax 2010; 65(6): 539-44.
Bronsveld I, Sinaasappel M, Southern KW, Sermet-Gaudelus I, Leal T, Melotti P, Ballmann M, Hjelte L, Middleton PG, De Boeck K, Wilschanski M. Evaluation of European protocols for measuring nasal potential differences. J Cyst Fibros 2009; 8(S2):10.
Derichs N, Bronsveld I, Sousa M, Hug MJ, Yaakov Y, Ballmann M, Amaral M, Wilschanski M, de Jonge H. Intestinal Current Measurement (ICM) in Europe: towards a harmonised protocol for clinical trials in cystic fibrosis. J Cyst Fibros 2009; 8(S2):123.
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Dequeker E, Stuhrmann M, Morris MA, Casals T, Castellani C, Claustres M, Cuppens H, des Georges M, Ferec C, Macek M, Pignatti PF, Scheffer H, Schwartz M, Witt M, Schwarz M, Girodon E. Best practice guidelines for molecular genetic diagnosis of cystic fibrosis and CFTR-related disorders-updated European recommendations. Eur J Hum Genet 2009;17(1):51-65.
Wilschanski M, Dupuis A, Ellis L, Jarvi K, Zielenski J, Tullis E, Martin S, Corey M, Tsui LC, Durie P. Mutations in the cystic fibrosis transmembrane regulator gene and in vivo transepithelial potentials. Am J Respir Crit Care Med 2006;174:787-94.
De Jonge HR, Ballmann M, Veeze H, Bronsveld I, Stanke F, Tümmler B, Sinaasappel M. Ex vivo CF diagnosis by intestinal current measurements (ICM) in small aperture, circulating Ussing chambers. J Cyst Fibros 2004;3 Suppl 2:159-63.
Schüler D, Sermet-Gaudelus I, Wilschanski M, Ballmann M, Dechaux M, Edelman A, Hug M, Leal T, Lebacq J, Lebecque P, Lenoir G, Stanke F, Wallemacq P, Tümmler B, Knowles MR. Basic protocol for transepithelial nasal potential difference measurements. J Cyst Fibros. 2004;3 Suppl 2:151-5.

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