ECFS – Diagnostic Network Working Group (DNWG)

Coordinator: Nico Derichs (Berlin, Germany)

Annual report, May 2017

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 85 members from 44 countries (Figure 1).

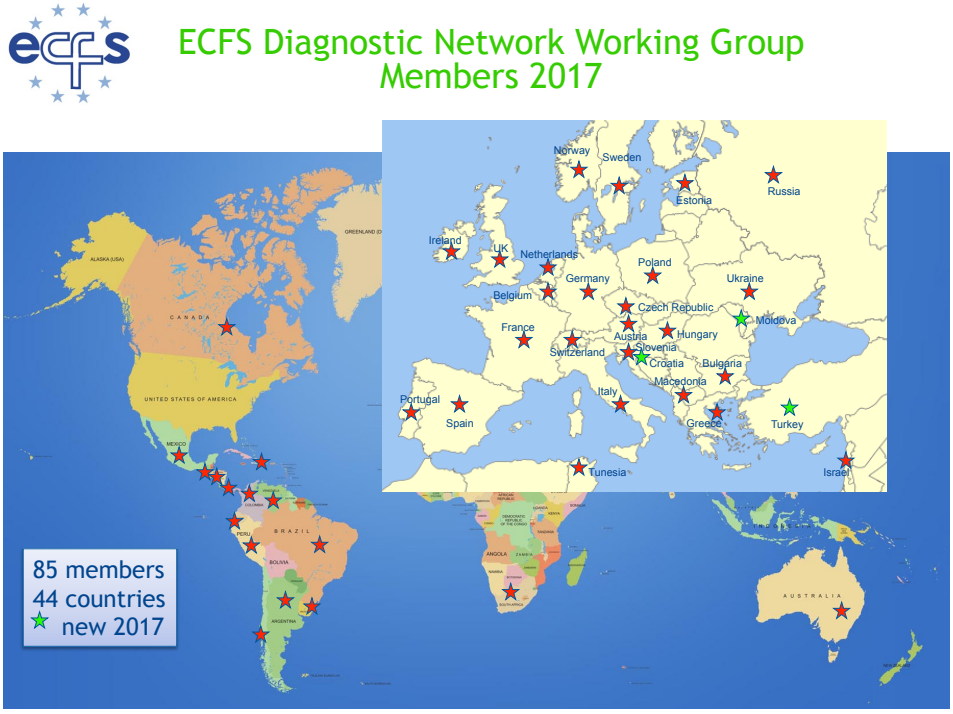

Figure 1. Overview of members (2017) within the ECFS Diagnostic Network Working Group.

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 2016 in Basel (open to all conference participants)
- Business meeting at NACFC 2016 in Orlando
- 14th Annual Group Meeting in Ljubljana, 16-18 February 2017 (see program and detailed report)

Special activities in 2016/2017:

- Participation in the CFF Diagnosis Consensus Conference and subsequent new guidelines (published in Feb 2017, see Figure 2)
- Participation in the Global Registry Harmonisation Group (Meetings at NACFC 2016 Orlando & ECFC 2017 Seville)

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 Neonatal Screening Working Group, ECFS Patient Registry, ECFS Clinical Trials Network, CF Europe, National Organisations

Next meetings:

- DNWG Meeting at ECFC in Seville, Friday 9 June 2017, 12:30 to 14:30 (open to all conference participants)
- DNWG Business meeting at NACFC in Indianapolis, November 2017
- 15th Annual ECFS DNWG meeting, February 2018

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.

Young Investigators:

We are actively promoting the involvement of Young Investigators to the DNWG group activities and oral presentations at the Annual group meetings. For the London 2016 meeting, we had presentations of 6 Young Investigators from Italy, France, Belgium, Germany, South Africa and Brazil. For the Ljubljana 2017 meeting, we had presentations of 4 Young Investigators from Israel, Netherlands, Germany and UK.

News, Activities, Projects:

DNWG CF Diagnosis Registry project (K. De Boeck)

The ECFS DNWG performed a project to evaluate current documentation of CF diagnosis in the CF registries and to connect the work of the ECFS DNWG and the ECFS Patient Registry. It was hypothesized that diagnosis data are incomplete e.g. due to changing techniques and terminology, lack of harmonized criteria for relevance of CFTR mutations and insufficient quality control systems.
Aim: To unambiguously define the population characteristics for inclusion and/or analysis in CF registries, especially when registry data are used for 'benchmarking' of centers or countries.

The ECFS DNWG CF Diagnosis Registry project is closely collaborating with the ECFS Patient Registry, National CF registries and Global Registry Harmonisation Project, and includes the following workpackages:

- Workpackage 1: Determine the scope of the problem: who is reported in national CF registries? *(K. De Boeck) – Results have been published*
- Workpackage 2: Measures to improve documentation of CF diagnosis in CF registries *(N. Derichs, L. Nährlich) – ongoing within the global harmonisation project*
- Workpackage 3: Are national registries with and without neonatal screening comparable? Is the cohort of patients younger than 8 years different in national registries with and without newborn screening? *(K. De Boeck, A. Munck) - finalised*
- Workpackage 4: How to define CF diagnosis by CFTR biomarker NPD and ICM *(M. Wilschanski, N. Derichs) – finalised, publication in preparation*

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. Publication of results is being planned within 2017.

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 is 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 (Workshop 11) and at the ECFS DNWG Meeting in Ljubljana 2017. A paper has been submitted to the Journal of CF in March 2017.

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.

CFTR3: Personalised characterization of rare Cystic Fibrosis genotypes (N. Derichs & Core Group)

- Aim: to newly establish a European database on the functional and clinical consequences of rare *CFTR* mutations/variants that are not possible to be characterised within CFTR2
- In synergistic addition to CFTR2, the CFTR3 project will use personalised characterisation of *in vivo* and *ex vivo* CFTR function in native human epithelia by 3-organ targeted CFTR biomarkers
- Rationale: a complete description of the basic disease defect and characterisation of rare *CFTR* gene variants/mutations can lead to a highly personalised medicine using diagnostic classification and clinical care as a typical example of patients stratification and providing a basis for new therapeutic approaches on an individualised level

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

Update of European CF Diagnosis Guideline (N. Derichs, K. De Boeck & Core Group)

- Core Group from ECFS DNWG and ECFS NSWG
- Development of statements and algorithms adressing the current status and open questions
- Delphi to all members of both Working Groups
- Open to input from external experts
- Recommendation to ECFS Board
- Update of 2006 ECFS Diagnostic Guideline
- Continue to work towards global CF diagnosis consensus

Latin American Newborn and Early Screening of Cystic Fibrosis Patients (LANES)

1st Expert Consensus Meeting in collaboration with the ECFS Diagnostic Network Working Group and Novartis

Objectives: Establishing an early diagnosis of CF in Latin America is suspected to be challenging due to several reasons, including heterogeneity of the population, availability and costs of diagnostic tests and lack of public awareness for CF in some countries.
Methods: An initiative by the ECFS Diagnostic Network Working Group aimed to better understand the current status of early CF diagnosis in Latin America. Expert representatives from 13 Latin American countries (Mexico, Guatemala, Costa Rica, Panama, Dominican Republic, Venezuela, Colombia, Ecuador, Uruguay, Brazil, Peru, Argentina, Chile) were invited to prepare a structured summary on the history and current situation of CF diagnosis in their country, and to share their experiences at the first Latin American Newborn and Early Screening of Cystic Fibrosis Patients (LANES) consensus meeting which was held in August 2015 in Sao Paolo, Brazil together with representatives from the ECFS DNWG and ECFS Patient Registry.
Results: Important differences and challenges in diagnosing CF were discussed, including epidemiology, CF newborn screening, sweat test, CFTR genotyping and use of CF registries.
Conclusion: The LANES project is the first joint initiative to summarise current practices and future perspectives for early CF diagnosis in Latin America. Increasing public awareness for early CF diagnosis was agreed to be of critical importance. Results from all attendees highlighted the significance and success of the LANES meeting, allowing for shared experiences to be discussed

and future relationships and collaborations to achieve the best outcomes for CF patients in Latin America.
Results of this project were presented at ECFC Basel (Workshop 11). Publication of results is being planned within 2017.

Publications:

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Figure 2. Involvement of the ECFS Diagnostic Network Working Group in the CFF Consensus Guidelines for Diagnosis of CF (J Pediatr 2017).

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):

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.
Mayell SJ, Munck A, Craig JV, Sermet I, Brownlee KG, Schwarz MJ, Castellani C, Southern KW; European Cystic Fibrosis Society Neonatal Screening Working Group. A European consensus for the evaluation and management of infants with an equivocal diagnosis following newborn screening for cystic fibrosis. J Cyst Fibros 2009;8:71-8.
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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