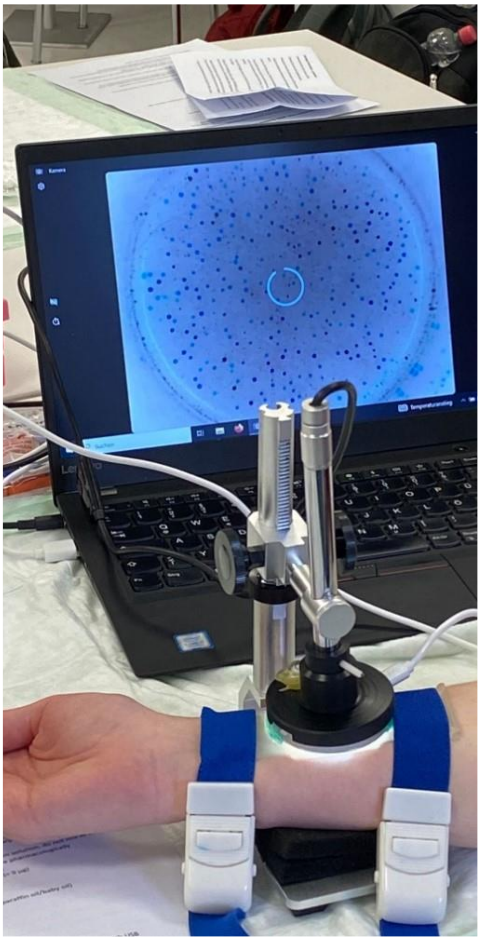
ECFS Diagnostic Network Working Group
Meeting Report

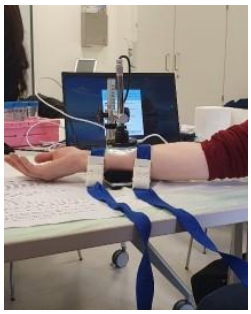
21st Annual Meeting, Hannover, Germany - February 8th - 10th 2024

Thursday, 8th of February 2024

Part 1. Hands-on sessions on beta-adrenergic sweat test

One of the highlights of the meeting was a hands-on session on the beta-adrenergic bubble sweat test, a novel diagnostic tool for cystic fibrosis under development. The session was presented and led by Manuel Nietert and Sophia Pallenberg, who demonstrated how the sweat bubble imaging assesses the cholinergic and ß-adrenergic sweat secretion. After the introduction, everyone got the chance to perform the beta-adrenergic sweat test themselves, under the guidance of Manuel and Sophia.





Part 2. Scientific Program

At 14:30 the meeting started with welcome words from Elke De Wachter and Nick Simmonds to the 60 participants of the 21st annual ECFS DNWG meeting in Hannover, Germany.

Session 1: Hannover's fondness for the CFTR protein and its function

Chair: Elke De Wachter (Brussels, Belgium) - Burkhard Tümmler (Hannover, Germany)

Frauke Stanke (Hannover, Germany) introduced CFTR glycoisoforms and their distribution in patients. She shared findings from a study that examined rectal biopsies from 21 cystic fibrosis (CF) patients carrying the p.Phe508del mutation, using CFTR Western blot analysis both before and during treatment with ELX/TEZ/IVA. The results indicated that while the treatment boosted the expression of the mutant *CFTR* protein, it did not enhance its glycosylation, a factor that may affect its long-term function and clinical benefit. Following this, *Anna-Maria* **Dittrich**, **Sophia Pallenberg**, and **Burkhard Tümmler** (Hannover, Germany) each presented a complex diagnostic case from the Hannover clinic. These presentations sparked an engaging and interactive discussion among the attendees, highlighting the complexities and nuances of diagnosing cystic fibrosis.

Session 2: Hannover's fondness goes beyond biomarkers alone

Chair: Nick Simmonds (London, UK) - Burkhard Tümmler (Hannover, Germany)

The second session started with a presentation by **Till Frederik Kaireit** (Hannover, Germany). He provided a detailed explanation of how phase-resolved functional lung MRI is used to study people with CF. Following him, **Ilona Rosenboom** (Hannover, Germany) discussed the cystic fibrosis upper and lower airway metagenome. She described how the study of the microbial metagenome in the airways of people with CF involved using whole-genome shotgun sequencing to examine the complete DNA taken from nasal lavage samples, throat swabs, and induced sputum samples. Her findings revealed that the heterogeneity of commensals varies between healthy individuals and CF.

Friday, 9th of February 2024

Session 3: Global CFTR genetics

Chairs: Debbie Morris-Rosendahl (London, UK) - Emmanuelle Girodon (Paris, France)

The second meeting day began with **Caroline Raynal** (Montpellier, France) discussing the quality of genetic data in national CF registries. She suggested a system to improve the quality of genetic data through data curation, analysis, and verification. Then, **Frauke Stanke** (Hannover, Germany) talked about the changing impact of CFTR gene modifiers over time. She highlighted the minor role of CF modifier genes compared to the environment. Next, **Emmanuelle Girodon** (Paris, France) presented two challenging cases in CF molecular diagnosis. The cases stressed the need for a comprehensive investigation of various criteria for evaluating variants' disease liability. She argued that epidemiological data should consider not only allelic frequencies in the general population but also observations in patient databases. Finally, the first Young Investigator, **Jasmin Berger** (Berlin, Germany), presented her study on primary nasal epithelial cells. She concluded that these cells are a promising tool for personalized medicine in patients with rare mutations and a possible additional component in the diagnosis of difficult cases.

Session 4: Update: ECFS standards on CFTR-related disorders

Chair: Chris De Boeck (Leuven, Belgium) - Carlo Castellani (Genoa, Italy)

The fourth session focused on the Diagnostic Network Working Group's update to the ECFS standards of care for CFTR-RD. **Carlo Castellani** (Genoa, Italy) introduced the first paper on the definition, evaluation, and management of CFTR-RD. **Isabelle Sermet** (Paris, France) summarized the second paper on the diagnostic criteria for CFTR-dysfunction in CFTR-RD. **Nicholas Simmonds** (London, UK) presented the third paper describing the individual disorders. **Elke De Wachter** (Brussels, Belgium) discussed the fourth and final paper on the critical challenges of CFTR-RD, such as data registry, genetic counseling, guideline implementation, and clinical trials. **Kevin Southern** (Liverpool, UK) spoke about the future management of CFTR-RD in his talk "A Man with a Plan". He stressed the need for disseminating the guidelines to healthcare professionals and suggested strategies such as registries and centralized diagnostic and management hubs. **Noelia Rodriguez Mier** (Leuven, Belgium) presented a case of a child with Pseudo-Bartter syndrome as a CFTR-RD. This led to a discussion on how pseudo-Bartter syndrome, mainly attributed to salt loss in sweat, can occur in infants with intermediate sweat chloride concentration levels. **Rihab Makhlouf** (Sfax, Tunisia), the second Young Investigator, shared her experience and challenges in sweat test practices in her laboratory in Habib Bourguiba Hospital.

Session 5: Newborn screening and CFSPID

Chair: Jürg Barben (St-Gallen, Switzerland) - Silvia Gartner (Barcelona, Spain)

Anne Munck (Paris, France) reviewed the progress in the last 10 years on CFSPID. She emphasized that most infants with CFSPID remain healthy and do not develop CF during childhood, hence the advice and management should reflect this reality. She advocated for the collection of long-term data and the establishment of a CFSPID registry to address unanswered questions regarding outcomes. **Jürg Barben** (St-Gallen, Switzerland) spoke on the future management of CFSPID in his presentation entitled "The bumpy road to a correct diagnosis that stands the test of time". Subsequently, **Simon Gräber** (Berlin, Germany) presented a case of a girl who tested positive for CF during newborn screening, with genetic analysis revealing a F508del/R347H genotype. Following this, **Seyda Karabulut** (Istanbul, Turkey) discussed a 3-year-old CFSPID case with variable sweat chloride levels and a heterozygous c.2991G>C (p.Leu997Phe) variant in the *CFTR* gene. Both cases highlighted the difficulties in interpreting genetic variations and underscored the importance of ongoing clinical and molecular evaluations for accurate diagnosis and management in CF patients.

Session 6: Small bubbles do matter!

Chair: **Burkhard Tümmler (Hannover, Germany) - Isabelle Sermet (Paris, France)**

Jeffrey Wine (Stanford, US) delivered a keynote lecture entitled "How the sweat gland reveals levels of CFTR activity." Unfortunately, Jeffrey Wine was unable to attend the meeting in person and therefore presented his talk remotely. In his lecture, he highlighted the significance of the sweat gland as a diagnostic tool for estimating CFTR activity through two primary methods: sweat chloride concentration and β-adrenergic sweat rate. He further clarified that these methods are complementary in their sensitivity to CFTR activity levels; sweat chloride concentration is most sensitive at lower levels of CFTR activity, whereas the β-adrenergic sweat rate provides greater sensitivity at higher levels of CFTR activity.

Saturday, 10th of February 2024

Session 7: Sweat testing

Chair: Paola Melotti (Verona, Italy) - Isabelle Sermet (Paris, France)

The final day of the meeting started with a remote presentation by **Natalia Cirili** (Ancona, Italy), who gave an update on the ECFS quality improvement program for sweat testing. This initiative aims to improve the quality of the performance of sweat testing in established and emerging CF services, including lower- and middle-income countries (LMIC) in and outside Europe. She summarized the work that has been done after the sweat test hands-on session that was held in Vienna at the ECFC 2023.

Next, the differences across Europe regarding the β-adrenergic sweat test as a diagnostic tool were highlighted through a series of expert presentations. The series kicked off with **Manuel Nietert** and **Sophia Pallenberg** (both from Hannover, Germany) elucidating the Hannover 'bubble' test. This was followed by **Paola Melotti** (Verona, Italy) sharing insights from her experience with the β-adrenergic sweat test in Verona. Next, **Angelique Mottais** (Brussels, Belgium) provided a comprehensive overview of the application of iontophoresis in β-adrenergic sweat secretion, as an alternative to intradermal injections. **Mairead Kelly-Aubert** (Paris, France) then delved into the nuances of evaporimetry as measurement tool for β-adrenergic sweat, highlighting the distinctions in technique and resultant data.

The session concluded with a presentation by **Dumitru Scutelnic** (Verona, Italy), the third Young Investigator, on his work on automated image analysis for the optical β-adrenergic sweat test, demonstrating the ongoing advancements in CF research and diagnostics.

Session 8: The Future of CF diagnostics – dilemmas about treatment

Chair: **François Vermeulen (Leuven, Belgium) - Simon Graeber (Berlin, Germany)**

Karin de Winter-de Groot (Utrecht, The Netherlands) provided an overview of the use of intestinal organoids as a diagnostic tool in the year 2024. Her presentation highlighted the advanced techniques and methods that show the potential of intestinal organoids in clinical diagnostics and personalized medicine. **Sophie Gohy** (Brussels, Belgium) captivated the audience with the presentation of a particularly challenging diagnostic case involving a 35-year-old woman who has the genotype F508del / V938G. This case illustrated the complex and detailed work needed in cystic fibrosis diagnostics.

Elke De Wachter (Brussels, Belgium) and **Nick Simmonds** (London, UK) brought the 21st Annual Meeting to a close with a comprehensive summary of the meeting. They took the opportunity to outline the future initiatives for the DNWG, beginning with a project that emerged from a brainstorming session in Phoenix in November 2023. This project aims to

establish a forum dedicated to addressing complex CF/CFTR-RD diagnoses, proposing regular team meetings every 2 to 3 months for DNWG members who are keen to participate. These sessions would focus on collaborative discussions about real-life case studies, fostering a vibrant community of practice. The practical feasibility of this proposal was a topic of lively discussion among the attendees. Next steps to operationalize this initiative were outlined.

Following this, Elke and Nick shared that their terms as coordinator and co-coordinator are nearing an end next year. Although Nick was prepared to step into the role of coordinator with a new co-coordinator, who would then succeed him after three years, he announced his inability to take on this responsibility due to other commitments. Consequently, they invited interested participants to apply for these two positions.

The meeting's hosts – **Burkard Tümmler, Sophia Pallenberg, Manuel Nietert** – along with all the sponsors, were warmly thanked for their exceptional organization of this successful event.

We thank all speakers and participants for their fantastic contribution to making the 21st Annual ECFS Diagnostic Network Working Group Meeting a great success! We are looking forward to meeting you at our next ECFS DNWG Meeting.

10th February 2024

Burkhard Tümmler – Local host
Sophia Pallenberg – Local host
Manuel Nietert – Local host
Elke De Wachter – ECFS DNWG Coordinator
Nicholas Simmonds – ECFS DNWG Vice-coordinator
Marlies Destoop – ECFS DNWG Assistant (author of the report)

ECFS DNWG Young Investigators 2024

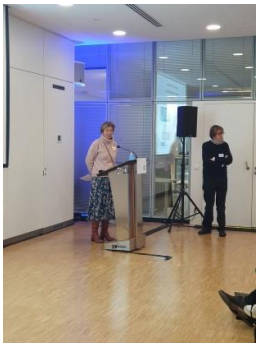
Jasmin Berger (Berlin, Germany)

Rihab Makhlouf (Sfax, Tunisia)

Dumitru Scutelnic (Verona, Italy)

ECFS Diagnostic Network Working Group 2024

Scientific program:



The meeting was kindly supported by: