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FOURTH EDITION

Hodson and Geddes'  
**Cystic Fibrosis**

EDITED BY

Andrew Bush • Diana Bilton  
Margaret Hodson



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# **Cystic Fibrosis**



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# Preface

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“Go and look it up in *Hodson and Geddes*” must be among the most common phrases heard in the CF clinic or ward round over the last many years. Duncan Geddes has stepped down as editor of this edition, and it will also be Margaret Hodson’s last volume. So in honor of these two giants in the field, this edition has been renamed *Hodson and Geddes’ Cystic Fibrosis*. This change was greeted with universal approval by all who were consulted, other than the two professors themselves, who were adamantly opposed to the change. For perhaps the only time in the life of the CF community, their views were ignored—and rightly so!

So why a new edition? This is an era of change in CF; new diagnostic methods—the advance of newborn screening, the recognition of milder and atypical phenotypes; new diagnostic techniques such as molecular microbiology; new approaches to conventional problems, and, more excitingly, the age of targeting the upstream defect, with gene therapy and designer molecular treatments, with their incredible benefit and even more incredible expense; and novel animal models—what will the ferret and pig teach us? So a big focus of this volume is clinical trials work; what we have got right, what went wrong, and what we can learn so we can do better in the future.

There are many innovations in this edition. Most obviously, for the first time we have a companion eBook. This eBook is automatically available to individuals who purchase the print book at no additional charge. To avoid any confusion, both versions are identical.

We have also included classic chapters from the previous edition—James M. Littlewood on the history of CF and Philip Robinson on the Melbourne approach to the newborn screened baby—both of which are well worth rereading and are found in the appendices. And two exciting new chapters that take a fresh look at these topics have been added; Kris De Boeck on the journey starting with the

discovery of the CF gene and an account of a UK protocol for the education visit for newborn screening. We have also shuffled the pack of our authors, making some of them stretch to write new chapters, as well as bidding a grateful and fond farewell to others; this has allowed us to bring in new contributors to challenge our thinking. A totally new innovation is a chapter written by patients and families—without doubt the most informative and challenging in the book. A special mention to Jessica Harrison—teenage girls get a bad press, but hers was the first contribution to be submitted, length perfect, and word perfect. Let no one badmouth teenagers ever again; would that some senior professorial persons (no names, but you know who you are, and so do we!) had followed her example! We sincerely hope that this combination of the best of the conventional, with the new horizons, makes this book a worthwhile read.

We must thank the publishers, and in particular Rachael Russell, for unfailing patience (even when taxed beyond the limit), enthusiasm, and support. The credit for the quality of the work is theirs; the blame for any errors which have slipped through belongs solely to us.

Finally, we want to mark with sadness the passing of a giant in the field, Gerd Döring. He has contributed to this and previous editions; his contributions to the field have been well-rehearsed elsewhere; suffice to say he will be sadly missed. As with another great German hero, Oscar Schindler, he is mourned in every continent.

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# Introduction: What is cystic fibrosis?

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# Introduction: From the discovery of the *CFTR* gene in 1989 through to 2014

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KRIS DE BOECK

The previous edition of this book commenced with a history of cystic fibrosis (CF) by Dr. Littlewood, up until the discovery of cystic fibrosis transmembrane conductance regulator (*CFTR*). This is available in the e-book form and has been further extended and is also available online via <http://cfmedicine.com/history>. This chapter will rather describe how, slowly, the entire field of CF was transformed by a continuous stream of knowledge, a new look at the diagnosis of CF, reorganization of clinical research, clinical care, and partnering.

A selection of the plenary lectures at the European cystic fibrosis conferences can serve as a guide for the shift in focus over the years (Table 1.1). The plenary lectures at the North American cystic fibrosis conferences, listed in Table 1.2, describe the parallel story on the other side of the Atlantic.

I describe how the European CF clinician experienced this period. It is difficult to understand that there indeed was a time when we treated patients with CF without knowing anything about the *CFTR* gene nor much about the basic defect in CF. Very many people contributed to the successes, but I will mention only a few people specifically. It is obvious that I have to oversimplify the story. For both facts, I apologize in advance.

**KNOWLEDGE: CF CLINICIANS LEARN ABOUT THE *CFTR* GENE, THE *CFTR* PROTEIN, AND CELL BIOLOGY**

## *CFTR* GENE CODE WAS FINALLY BROKEN

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The knowledge of the entire base sequence of the *CFTR* gene and the description of the common mutation *F508del* brought a lot of excitement in the early 1990s, including the belief that a cure via gene therapy would soon be available. However, many hurdles to gene therapy lined up. In patients with CF, efficient gene transfer proved difficult and was not

without risk: the large size of the *CFTR* gene is problematic, adenoviral vectors can cause severe inflammation, antibodies to viral vectors impair efficacy with repeated administration, and adenoviral receptors are located mainly at the less exposed basolateral epithelial cell surface. The hype leading to the belief that gene therapy would soon (within the 1990s) bring the solution for patients with CF ebbed down.

## NUMEROUS *CFTR* MUTATIONS WERE REPORTED

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*CFTR* mutation after *CFTR* mutation was being described. The enormous genetic heterogeneity of the disease was recognized. Although this led to explaining part of the heterogeneity in disease severity, a landmark paper from Eitan Kerem et al.<sup>1</sup> shattered the notion of a simple correlation between genotype and phenotype. Pancreatic phenotype seemed largely driven by genotype, but individual homozygous *F508del* patients appeared to have a vast difference in lung disease severity, pointing from the start to the importance of genetic modifiers and the environment.

Given this genetic heterogeneity, gene therapy remained an attractive option, especially to improve CF lung disease, an organ accessible via aerosol inhalation. So, a few groups, the UK gene therapy consortium most prominently, continued in this field of gene therapy and explored the use of nonviral vectors. Their effort led to the phase 2b trial with monthly applications of gene therapy in 200 patients, a landmark trial from which the first results are eagerly awaited.

## FIRST CARTOONS OF THE *CFTR* PROTEIN EMERGE

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The rather unexpected great complexity of applying gene therapy in CF had shifted much of the focus to the *CFTR* protein. The resemblance of the 'anticipated' structure of the *CFTR* protein to the ABC transporters made the chloride

Table 1.1 ECFS plenary lectures

Year	City	Plenary title	Speaker
1991	Copenhagen	Gene therapy in CF	Crystal RG
1993	Madrid	Spectrum of mutations in cystic fibrosis	Estivill X
1994	Paris	Gene therapy: Results of first clinical trials Pharmacotherapy for abnormal ion transport in CF: Aerosolized amiloride and uridine triphosphate	Crystal R Knowles M
1995	Brussels	CF in the mouse and gene therapy in man Changes in genetic counseling strategies for CF	Porteus DJ Brock DJH
1997	Davos		
1998	Berlin	Gene therapy Gene targeting: Prospects for CF gene therapy	Geddes D Gruenert DC
1999	The Hague	How do we link CF ion transport defects to CF lung disease?	Boucher RC
2000	Stockholm	The CFTR protein: Function and dysfunction, processing and misprocessing	Riordan JR
2001	Vienna	The <i>CFTR</i> gene Genetic modifiers of CF—the emerging picture Gene therapy—where we are, where are we going?	Cutting G Zielenski J Hyde S
2002	Genoa	Patients' segregation pros Patients' segregation cons	Koch C Geddes D
2003	Belfast	How should we screen for CF? New treatments for CF	Farrel P Geddes D
2004	Birmingham	Atypical CF Phenotype: Genes or environment Genetic counseling	Knowles M Cutting G Super M
2005	Crete	The latest CFTR research How to correct the basic CF defect in mice How pathogens cause lung infection and inflammation How to treat airway infection in the future	Amaral M Gulbins E Döring G Høiby N
2006	Copenhagen	Therapy for CF based on a rational understanding of CFTR	Sheppard D
2007	Belek	Anti-inflammatory treatment: How far can we go? How do we assess therapeutic benefits? Is newborn screening for CF a basic human right?	Elborn S De Boeck K Farrell P
2008	Prague	What do we still need to know to stop CF lung damage: CFTR dysfunction Infection Inflammation Options to treat	Amaral M Döring G Accurso F Davies J
2009	Brest	Clinical trials: Priorities and challenges Patient organizations' contributions to clinical research	Tiddens H Dufour F
2010	Valencia	Restoring CFTR function in CF airways Current treatments for CF to prevent disease progression	Boucher R Stick S
2011	Hamburg	Models of inflammation: From bench to bedside Genotype-phenotype in CF: Implications in CF care	Mall M Durie P
2012	Dublin	Inflammation and infection, lessons from the CF pig model Potentiating and correcting CFTR	McCray P De Boeck K
2013	Lisbon	CFTR2 The importance of understanding genotype Delivering quality care in CF. New challenges and solutions?	Cutting G Bilton D
2014	Gothenburg	Mucus – The central problem in CF Preventing and treating pulmonary exacerbations	Hansson GC Flume P

Source: Courtesy of H. Riley and C. Dubois, ECFS office.

Table 1.2 Plenary lectures at the North American cystic fibrosis conferences

Year	Plenary title	Speaker
1989	The CF gene Advances in medical treatment of cystic fibrosis A look toward the future	Collins FS, Riordan J, Tsui L-C Rosenstein BJ Boucher RC, Wilson JM
1990	The CF gene one year later Gene therapy and model systems Immunopathology and new approaches to therapy	Collins FS, Riordan J, Tsui L-C Caskey CT, Crystal RG Berger M, Hoiby N, Moss R, Suter S
1991	The CF gene two years later: Progress and projections New frontiers in therapy	Collins FS Crystal RG
1992	The CF gene: Perceptions, puzzles and promises The new pharmacology: Tools to arrest CF lung disease Gene therapy in CF: Progress and prognosis: In vivo gene transfer strategies for the respiratory manifestations of cystic fibrosis Strategies for gene therapy of CF	Collins FS Boucher RC  Crystal RG  Wilson JM
1993	The CF gene: Old questions, new insights CF: Electrolyte transport revisited Gene therapy for CF: A glimpse into the future	Collins FS Welsh MJ Boucher RC, Crystal RC, Whitsett JA, Wilson JM
1994	Understanding cystic fibrosis: Accomplishments and challenges on the road to a cure Advances in clinical science and management Prospects for human gene therapy of cystic fibrosis	Welsh MJ  Davis PB Wilson JM
1995	1995: The year in review Clinical advances in CF: Recognizing the cure Human gene therapy for CF: Lessons learned & hurdles to success	Collins FS Davis PB Crystal RG
1996	CF research: Highlights of 1996 The immune system: The devil within of the good guy? On track with CF gene delivery vehicles	Collins FS Wilson CB Wilson JM
1997	CF research: The best of 1997 New clinical developments in CF: From the test tube to the bedside Gene therapy for CF: Where have we been and where are we going?	Collins FS Ramsey BW Crystal RG
1998	The best of 1998 CFTR structure & function: pathophysiologic insights & novel targets for pharmacotherapies The CF cure: How close are we?	Taussig LM, Tsui LC Guggino WB, Hanrahan JW  Cantin AM, Davis PB
1999	The best of 1999 The process of drug discovery—an enlightened journey New clinical interventions	Boucher RC Beall RJ, Campbell PW Ramsey BW
2000	The best of 2000 CFF mission and vision Solving the puzzle: CF clinical research 2000	Wine JJ Beall RJ, Campbell PW Accurso FJ
2001	The best of 2001 Why won't they do what we tell them to do? Understanding families and understanding adherence CF clinical research: A journey with a destination	Welsh MJ Bluebond-Langner Myra, Lask B  Cantin AM
2002	CF airways pathophysiology: CFTR & beyond Changes in the natural history of CF from a GI perspective Developing better therapies for patients with CF: 2002 Progress report	Boucher RC Durie PR Ramsey BW
2003	From genes to drugs: The CF master plan Providing exemplary care: A partnership for change Disease progression in CF: Can we gain the upper hand?	Collins, Beall RJ, Ashlock MA O'Connor, Marshall BC Moss RD

(Continued)

Table 1.2 (Continued) Plenary lectures at the North American cystic fibrosis conferences

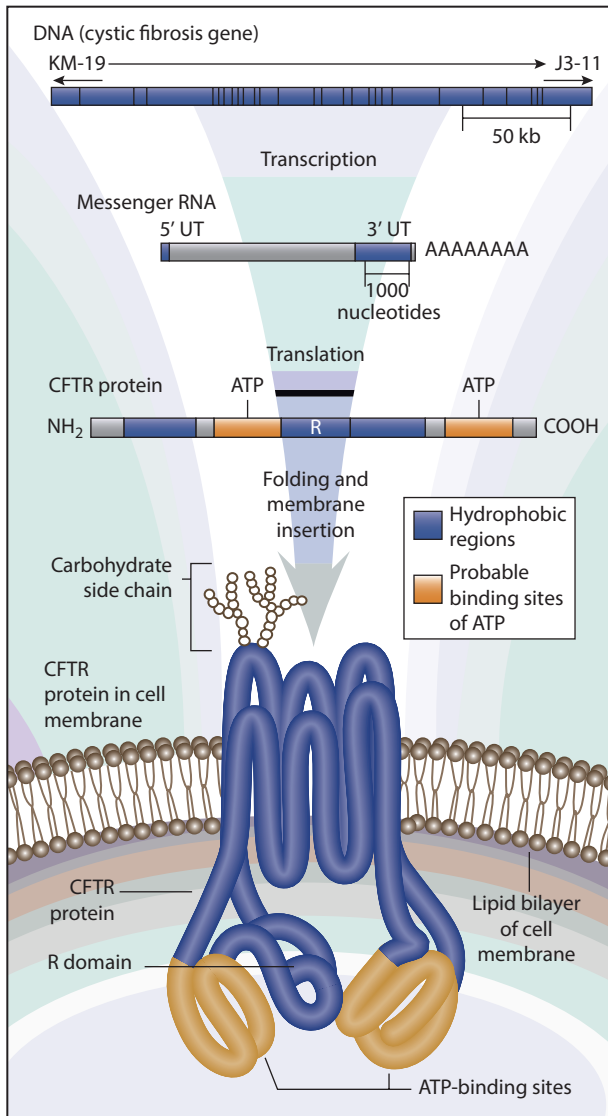
Year	Plenary title	Speaker
2004	Developing CF therapies: From the laboratory to the patient How do we recognize a clinically effective new treatment? Care providers and people with CF: Together we can make great things happen!	Davis PB, Konstan MW Alton E Batalden P, Acton JD, Page HO
2005	50 years of CF: Milestones to a cure 50 Years of CF clinical trials research: Accelerating the progress CF nutrition: Opportunities for the scientist & the care team	Campbell PW, Beall RJ Goss CH Borowitz D
2006	Promises to keep: Turning discoveries into drugs Clinical research: Our compass to a cure CF pulmonary care: Measuring & improving our effectiveness	Davis PB Clancy JP Yankaskas JR
2007	From basic science to the clinic: Where are we and what is still missing? CF drug development: What's new? Improving patient outcomes using the tools we have now	Amaral MD Ratjen F Boyle MP
2008	Preventing CF lung disease The CFF pipeline: The amazing story of progress, hope, and challenge Taking the CF battle to the extremes: Healthy starts with newborn screening; healthy aging with improved adult care	Wine JJ Campbell PW Farrell PM, Simon RH
2009	Two decades of CFTR research: From gene discovery to therapeutic target Inflammation & infection: Update on the pipeline Early airway infection in young children with CF—what is the optimal therapy?	Collins FS, Rowe SM Konstan MW Ramsey BW, Retsch-Bogart G, Wainwright CE
2010	Pipeline: Airway surface liquid modulation Animal models Transforming CF healthcare: Partnership for life	Sorscher E Stolz DA Berwick D, Marshall BC
2011	CFTR modulation—25 years of NACFC progress CFTR 2—a research & clinical practice tool Pulmonary exacerbations	Mall MA Cutting GR, Sosnay P Flume PA
2012	Reversing the basic defect: A vision for the future Advances in GI aspects of CF Adherence ... Where's the app for that?	Rowe SM, Skach W Borowitz D Riekert KA
2013	Restoring CFTR Function: Roadmap to a Cure (Part 1) Roadmap to a Cure (Part 2) Clinical Research Pathway to Ensure That All Patients With CF Benefit From Novel Therapies CFRD: From Bench to Bedside & Back Again (Care)	Donaldson SH Ramsey BW Engelhardt JF Kelly A
2014	Scaling the Mountain: The Journey to Delivering Transformational CF Therapeutics CF Microbiology Past, Present, Future CF Advisory Board Track: From Codman to Collaboratories: A Care Model for CF That's Fit for the Future	Boyle M LiPuma J Nelson E

Source: Courtesy of P. Campbell and CFF office

transport function logical and confirmed the previously documented chloride impermeable epithelium as (one of) the basic defects in CF. The presence of an R domain, unique in the ABC transporters, led to speculation about its function in opening and closing the channel pore. We saw the first cartoons depicting the CFTR protein (Figure 1.1): two membrane-spanning domains (MSDs), two nucleotide-binding domains (NBDs), and the enigmatic R domain. We heard the cell biologists discuss whether the protein is expressed at the cell surface as a monomer, a dimer, or even a tetramer.

## NEW KNOWLEDGE LED TO THE PARADIGM OF CYSTIC FIBROSIS PATHOPHYSIOLOGY

The pathophysiologic cascade of CF was described: from faulty *CFTR* gene, via abnormal CFTR protein, over disturbed ion flux, dehydrated airway surface liquid, and impaired mucociliary clearance to cycles of airway obstruction, chronic lung infection, and excessive inflammation, ultimately leading to organ dysfunction. This useful paradigm has remained



**Figure 1.1** Early cartoon depicting the different domains of the cystic fibrosis transmembrane conductance regulator protein.

a constant feature in CF presentations (Figure 1.2). The beauty was that a putative or existing therapy could be put at every level. Each individual scientist or clinician could position his project in this “cascade” without forgetting the overall picture. Increasingly as time went by, therapeutic targets have been focused upstream toward the basic defect as you will read here.

Viscous secretions and disturbed mucociliary clearance gave credence to the disease’s old name of “mucoviscidosis.” The clinicians left it to the basic scientists to unravel whether the “low volume” or the “high salt” hypothesis could explain the dehydrated airway surface liquid.<sup>2,3</sup> In the high salt hypothesis, a hypertonic airway surface liquid destroys the salt-sensitive natural antimicrobial molecules or defensins, thereby linking the dehydrated epithelium to CF’s impaired lung defense. Attempts to measure the exact salt concentration in the epithelial lining fluid left room

were fraught with difficulty, and the results were controversial. Currently, the low volume hypothesis is favored.

But the CFTR was discovered to be more than just a chloride channel: bicarbonate, hypothiocyanate, and other anions were also transported.<sup>4-6</sup>

## IMPORTANCE OF ION CHANNELS OTHER THAN CFTR WAS RECOGNIZED

Because the CFTR protein is embedded in the cell membrane next to other ion channels, the hierarchy in this potpourri of receptors was studied. Manipulating CFTR’s partners became a new therapeutic goal. The first attempts were to manipulate the epithelial sodium channel ENaC, overactive in the absence of CFTR and amenable to down-regulation by blockers such as amiloride. But the first clinical trial failed, the failure being attributed to amiloride’s short-lived action.<sup>7</sup> Although, in recent years, the CF pig model questions the theory of ENaC hyperactivity,<sup>8</sup> the search for safe and effective long-acting ENaC blockers continues. The pioneering work on ENaC by the German group with Greger, Kunzelmann, and Mall culminating in the development of a  $\beta$ -ENaC overexpressing mouse model deserves specific mention.<sup>9</sup> In an interventional study with amiloride in this mouse model, they pointed out that efficacy was only seen with preventive therapy and not with rescue therapy.

In addition, a mistaken hypothesis in a previous paper came to light. In the presence of amiloride, nucleosides applied to the cell surface were found to activate the defective chloride transport path in CF, possibly via the CFTR protein itself.<sup>10</sup> Because it was later found that in “classic CF” the CFTR protein is not present at the cell membrane, this stimulation could only occur via “alternative” chloride channels. A new drug target was born. Denufosal, a purinergic ( $P_2Y_2$ ) agonist stimulating chloride secretion via these alternative chloride channels, seemed promising in phase 2, but robust clinical efficacy was absent in phase 3 studies.<sup>11,12</sup> In the mean time, these alternative chloride channels have been nailed down as the TMEM16A proteins.<sup>13</sup>

## CFTR MUTATION CLASSES: THE LINK BETWEEN MUTATIONS AND PROTEIN

CFTR mutations were grouped in six classes according to their effect on the synthesis and function of the CFTR protein.<sup>14</sup> Another classic CF slide was introduced (Figure 1.3). Because the most common mutation *F508del* belongs to class 2, whereby protein misfolding leads to degradation in the proteasome, an intense study of CFTR folding started, including the formation of a CFTR folding consortium. This had the enormous advantage of bringing in existing knowledge such as “high throughput screening,” as well as building CFTR-specific knowledge.

Clinicians embarked on genotype–phenotype studies to link mutation class to disease pattern.<sup>15</sup> We learned

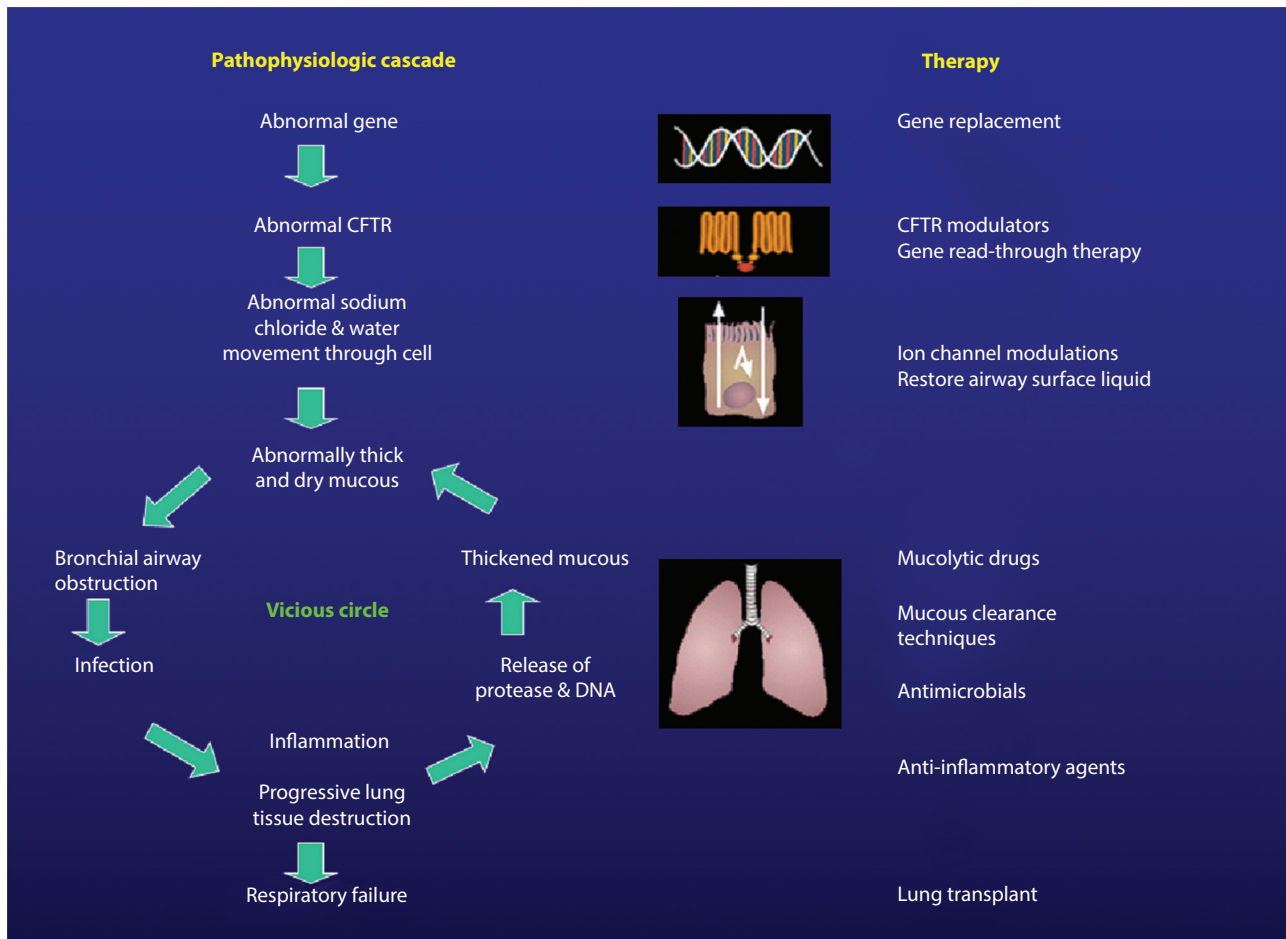


Figure 1.2 Paradigm of cystic fibrosis pathophysiology plus listing of putative and existing therapies to improve or prevent lung disease.

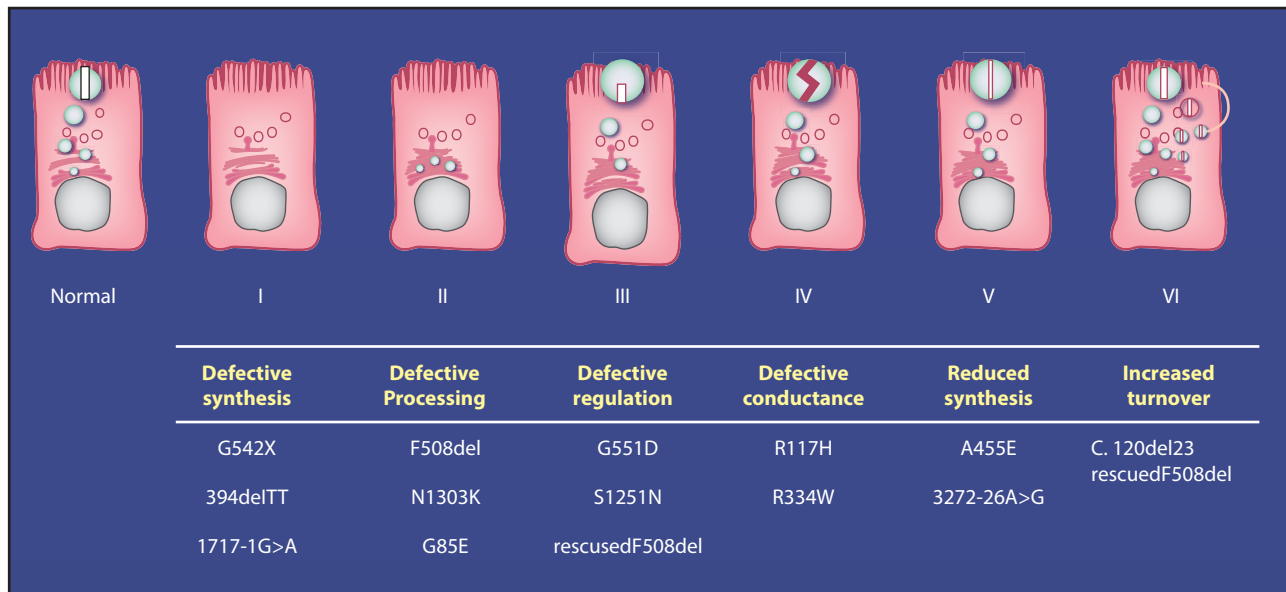


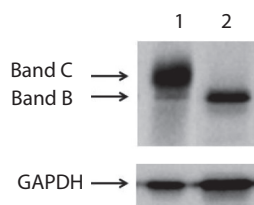
Figure 1.3 Cystic fibrosis transmembrane conductance regulator (*CFTR*) mutations are grouped in classes according to how the *CFTR* mutation interferes with CFTR protein synthesis or function. (Adapted from Amaral, M, and CM Farinha, *Curr Pharm Des*, 19(19), 3497–508, 2013.)

that having at least one class IV or V mutation can attenuate the clinical picture. Plausible, because in classes IV and V, CFTR protein is present at the cell membrane, be it either with decreased conductance (class IV) or in reduced amount (class V). Unfortunately, patients with two so-called “severe” mutations, namely, classes I (no synthesis), II (degradation), and III (no channel opening), greatly outnumber patients with at least one “mild” mutation of class IV or V.

Although useful for group predictions, the heterogeneity between individuals in the same mutation class proved to be vast, again pointing toward the importance of gene modifiers and the environment. Cleverly designed twin and sibling studies quantified the relative impact of these.<sup>16,17</sup> Different groups uncovered several modifier genes, but in later years genome-wide association studies were performed.<sup>18</sup> So far, these revealed few modifier genes with a major impact on disease outcome. The real challenge is of course to transpose the knowledge on modifier genes (and environment) to new therapeutic strategies.

## WE LANDED IN THE EXCITING ERA OF CORRECTORS AND POTENTIATORS

The complex folding and trafficking process of CFTR protein soon became an intense object of study by many, including a group in Lisbon headed by Margarida Amaral. En route through the endoplasmic reticulum, the immature CFTR protein is first partially (band B) and then fully glycosylated and recognized as “band C” in western blot (Figure 1.4). CFTR undergoes folding during synthesis. The protein encounters multiple checkpoints and makes contact with multiple binding partners or chaperones as well as nonchaperones. The description of the entire CFTR interactome was a major step forward.<sup>19</sup> Errors in CFTR processing result in degradation via the proteasome. The huge complexity of CFTR folding during transcription and post transcription has meant that correcting this proves to be a much more major task than was first thought.



**Figure 1.4** Western blot of cystic fibrosis transmembrane conductance regulator (CFTR) protein. Western blot of wild type (left) and *F508del* (right) CFTR protein expressed in BHK cells. In wild-type CFTR expressing cells, a prominent upper band, also called band C (corresponding to the fully glycosylated or mature form of CFTR), and a lower band, also called band B (corresponding to the immature, only partially glycosylated CFTR protein), are seen. In *F508del* cells, only band B is present (band C is absent), indicating that the mutant protein has not undergone maturation. (From Amaral M and CM Farinha, *Curr Pharm Des*, 2013; 19(19): 3497–508.)

In *F508del* CFTR cell lines, the protein is not present at the cell’s brush border but remains distributed diffusely in the cytoplasm. Increased appearance of CFTR protein at the cell surface after exposure *in vitro* to cold (23°C) was a first step in the search for “correctors,” compounds that increase the amount of CFTR at the cell surface.<sup>20</sup> The technique of high throughput screening based on advances in robotics and high-speed computer technology greatly helped the search for effective correctors: in these automated systems and by coupling CFTR to a yellow fluorescent protein-based halide sensor, thousands of chemical compounds could be tested overnight for their ability to activate CFTR chloride transport in, e.g., *F508del* cell lines. In Europe, Luis Gallieta was very active in this search for CFTR modulators. Several chemical correctors were evaluated such as phenylbutyrate, sildenafil, vardenafil, and genistein; the latter was later on considered as a potentiator. These compounds made it to the first stages of clinical development, but their efficacy was only modest. Eventually, the more potent corrector VX-809 was developed. After proof of concept in phase 2, this compound was being tested in phase 3 clinical trials, in conjunction with the potentiator VX-770. Indeed, when the *F508del* CFTR protein was “rescued” to the cell surface by corrector VX-809, the rescued protein channel’s open probability is decreased and this can be enhanced *in vitro* by potentiator VX-770. In patients with CF and *F508del* mutations combined therapy with corrector plus potentiator has modest efficacy.<sup>21</sup>

According to recent information, very efficient correction of misfolding may require at least a two-step correction approach: improving the folding and thermal stability of the protein as well as improving the linking of MSDs with NBDs via the intracytoplasmic loops (ICLs).<sup>22,23</sup> Apparently, the absence of phenylalanine at position 508 in NBD1 leaves a pocket that needs to be filled to restore the interface between NBD1 and ICL4. For optimal efficacy, other interactions, e.g., between NBD2 and MSD1 and between NBD1 and NBD2, may also need to be corrected. The mechanism of action of correctors identified via high throughput screening is mostly unknown. It is reassuring that an “intelligent” search for correctors with additive mechanisms of action, complementing the high throughput screens, has already started.

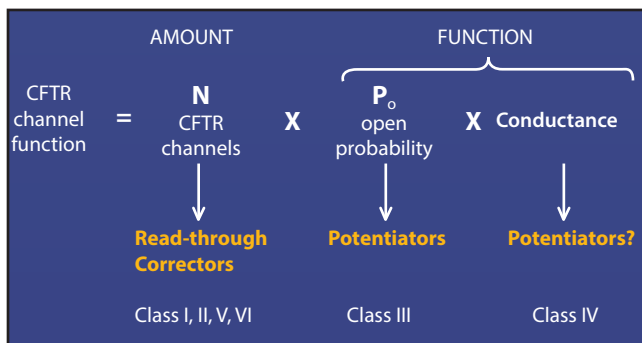
The highly dynamic process of opening and closing the CFTR protein was also being studied in great detail. The group in Bristol headed by David Sheppard made major contributions in this field. For a recent discussion of adenosine triphosphate (ATP)-dependent as well as ATP-independent mechanisms of CFTR channel opening and new insights into the configuration of the CFTR pore, see the study by Hwang and Kirk.<sup>6</sup> Clinicians learned about the classical “nutcracker” theory of opening the CFTR pore. Phosphorylation brings more structure to the bulky R domain, which thereby “moves out of the way.” Phosphorylation and ATP binding and hydrolysis at the NBDs lead to their dimerization. This in turn transmits—via the intracytoplasmic loops—a configurational change driving the MSDs apart: chloride or other anions can then pass. But this passage is short-lived: the reverse process takes place by dimerization of MSDs and

opening of NBDs until a new cycle starts. But channel opening is apparently much more complex and can also occur independently of ATP binding.

The discovery of VX-770 (later named ivacaftor), a *CFTR* potentiator that increases the *CFTR* channel's open probability, was a major breakthrough. The compound's in vitro efficacy was confirmed in vivo (Kalydeco®) in patients carrying at least one *G551D* mutation, the most common class III mutation.<sup>24</sup> Ivacaftor became the first drug on the market that improves patient outcome by improving the basic defect of CF, a true milestone in CF drug development and the first piece in the difficult puzzle of “curing CF”. Although it should be noted that pancreatic insufficiency remains in these patients and whether ivacaftor will prevent the development of later complications, such as CF-related diabetes and bone disease, remains to be seen.

Efficacy of ivacaftor has been proven in other class III mutations, which are responsive in vitro.<sup>25–27</sup> But there may be more indications for treatment with potentiators than patients with class III mutations only. In vitro ivacaftor potentiates wild-type *CFTR* and several mutant forms of *CFTR* of classes IV and V. The mutation class theory thereby needs revision. Many mutations have indeed characteristics of more than one conventional mutation class. In a new paradigm (Figure 1.5), we think of *CFTR* function as the product of the number of *CFTR* channels (typically disturbed in classes I, II, and V) and the function of the *CFTR* channel, the latter being dependent on the open channel probability (disturbed in class III and in rescued mutant *CFTR*) and the channel conductance (typically disturbed in class IV). Correctors and stop codon read-through drugs increase the number of *CFTR* proteins, and potentiators increase *CFTR* function opening. Strategies that target the *F508del* mutation at the mRNA level are also under development. Thus, multiple novel therapies may need to be tailored to individual mutations.

Also for patients with premature stop codon mutations, correction by ataluren, a compound aimed at overreading these premature stop codons, is being pursued.<sup>26,28</sup> In the phase 3 clinical trial the primary outcome of improvement in FEV1 was not reached.<sup>29</sup>



**Figure 1.5** Current paradigm linking defects in cystic fibrosis transmembrane conductance regulator (*CFTR*) protein function or synthesis and *CFTR* mutation classes with potential therapies by *CFTR* modulators.

## MODEL SYSTEMS: THE CF MOUSE, THE CF PIG, THE CF FERRET, AND ORGANOIDS

After the discovery of the *CFTR* gene, a CF mouse model was developed. Although it brought knowledge on inflammation and infection in CF lung disease, the fact that the CF mouse does not spontaneously develop lung disease was a major drawback. The CF pig, CF ferret, and CF rat took a much longer time to develop but proved to be excellent animal models for early CF lung disease, as they reflect lung disease in humans much better compared to the CF mouse model.<sup>30</sup> The CF pig becomes infected with a myriad of bacteria,<sup>31</sup> has abnormal airway cartilage,<sup>32</sup> and has a disturbed growth hormone axis.<sup>33</sup> These same abnormalities were documented in infants with CF. The CF pig model points toward the importance of bicarbonate not only in the gut but also in the lung surface liquid.<sup>34</sup> This knowledge will likely lead to new therapeutic options.

In the past year, an exciting new tool surfaced in the Netherlands: organoids, grown from rectal biopsies in patients.<sup>35</sup> This might open the possibility of individualized assessment of the efficacy of *CFTR* modulators in patients with rare *CFTR* mutations.

## DIAGNOSIS OF CYSTIC FIBROSIS NEEDED TO BE REVISED

### DIAGNOSTIC CONSENSUS, DIAGNOSTIC ALGORITHM, AND *CFTR*-RELATED DISORDERS

The diversity of *CFTR* mutations raised a new question: “what is cystic fibrosis?” The old definition of CF as a severe autosomal recessive disease characterized by changes in the lung, gastrointestinal tract, sweat gland, and male reproductive tract proved insufficient. *CFTR* mutations had been described even in adults with minimal disease expression or single organ disease. How much disease expression should be there before it is warranted to state that a person is suffering from CF? Indeed, labeling a person with the diagnosis of CF impacts not only health and treatment but also social functioning and well-being. A new definition of CF was proposed and revised later on with small differences between the United States and Europe.<sup>36–38</sup> But all agreed that the diagnosis must be supported by the presence of classical CF symptoms (or a sibling with CF or a positive newborn screening [NBS] test) plus two positive pilocarpine sweat tests (or the presence of two CF disease-causing mutations or an abnormal nasal potential difference or intestinal current measurement).

Because several diagnostic tests became available, a European algorithm was drafted to guide the clinician in the CF diagnostic pathway.<sup>37</sup> Some were unhappy with these algorithms, because in difficult cases results of diagnostic

tests may be discordant and because “CF is a continuum rather than a yes/no condition.”

The CFTR2 project ([www.CFTR2.org](http://www.CFTR2.org)) led by Garry Cutting was set up to answer some of the uncertainties about “CF-causing mutations,” by exploring existing patient registries and describing the phenotype of patients with *CFTR* mutations with a frequency above 0.01%.

More confusing was the notion of “CFTR-related disorders,” the term used for subjects with symptoms suggestive of CF but who do not meet diagnostic criteria.<sup>39</sup>

## NEWBORN SCREENING FOR CYSTIC FIBROSIS BECOMES THE STANDARD

NBS for CF was carried out prior to knowledge of *CFTR* mutations. Long-standing programs based on immunoreactive trypsin (IRT) measurements had proved the feasibility of NBS, as well as its long-term benefit on nutritional outcome.<sup>40</sup> Algorithms combining IRT with DNA analysis for the most common *CFTR* mutations in the target region greatly improved the efficacy of the program, by avoiding recall of many patients with falsely elevated IRT. In parallel, the advantages and lack of disadvantages of NBS became clearer. Algorithms for NBS were adopted in an increasing number of countries. European guidelines were drafted for how to organize NBS as well as how to manage infants with CF.<sup>41,42</sup> Opinions and governments differ in their approach to CF carrier detection. Some see it as an advantage if used for cascade screening and others as a disadvantage if revealing the carrier status of a baby is considered unethical.<sup>43</sup> A three-tier algorithm with IRT, DNA, and pancreas-associated protein greatly reduces detection of carriers and can also be considered.<sup>44</sup>

But there is no progress without new questions resulting. An unexpectedly high number of babies detected via NBS had the genotype *R117H-7T/F508del* and did not develop symptoms during childhood.<sup>45</sup> And what to do with babies who are screen positive but have an equivocal diagnosis of CF?<sup>46</sup> Do they truly deserve the strange name of “CFTR-related metabolic syndrome” chosen on the other side of the Atlantic?<sup>47</sup> And, although CF screening uses excellent and increasingly sophisticated methods, they are screening and not diagnostic tests.<sup>48</sup> Clinicians must remember that some patients will be missed by NBS.

## CYSTIC FIBROSIS CLINICAL RESEARCH HAS METAMORPHOSED

### A MASTER PLAN APPROACH CHANGES CLINICAL RESEARCH

Over the past 25 years, CF clinical research has changed from artisan patchwork to an entrepreneurial exercise with full attention to decisiveness. For too long, clinical research had mainly been thought provoking. Bright research ideas

were put forward, but the unequivocal proof of evidence was often lacking.<sup>49</sup> A good example of a large-scale CF trial of the modern era was the study of the efficacy of rhDNase.<sup>50</sup>

Efficient translation of the improving knowledge about CF to better treatments demanded a different approach. The birth of the therapeutic development network (TDN) in the United States in 1998 was a giant step in a new direction.<sup>51</sup> Large-scale, well-designed clinical trials with decisive answers became the new standard: among others, inhaled tobramycin, DNase used as early intervention, oral azithromycin, and EPIC.<sup>52–55</sup> A European example of research organization, the UK gene therapy consortium, was founded in 2001 (<http://www.cfgenetherapy.org.uk>). Inspired by the successful TDN, the European Cystic Fibrosis Society Clinical Trials Network (ECFS-CTN) ([www.ecfs.eu/ctn](http://www.ecfs.eu/ctn)) was formed in 2008. This initiative of the European Cystic Fibrosis Society received great support from the Cystic Fibrosis Foundation (CFF) and from the CFF-TDN. It was also supported by the European CF patient associations. Similarly, in Australia a CF-specific research network was formed with focus on disease in the preschool child (<http://arestcf.org>).

A master plan approach to clinical research became the obvious need. First, CF patient data registries were explored and the major challenges in CF, such as the age at fastest lung deterioration, impact of pulmonary exacerbations on lung disease progression, and identification of the most important CF complications, were defined. Second, CFF built a therapeutic pipeline ([www.CFF.org](http://www.CFF.org)) and prioritized the research of *CFTR* modulators.

### NEED FOR NEW OUTCOME MEASURES IS RECOGNIZED

The rational approach to clinical research was accompanied by a much closer attention to outcome parameters: standard operating procedures, adequate assessment of study feasibility, and power calculation.<sup>56</sup>

With improved CF treatments, we became the victims of our own success. Because the rate of lung function decline had become small, forced expiratory volume in 1 second (FEV<sub>1</sub>) was no longer an easy to use surrogate outcome parameter.<sup>57,58</sup> More sensitive outcome measures were studied in great detail. Proving the usefulness of computerized chest tomography with quantification of bronchiectasis, air trapping, and bronchial wall thickening became the mission of the Dutch group headed by Harm Tiddens.<sup>59</sup> Lung clearance index, a parameter of gas mixing efficiency, more sensitive than routine spirometry, was introduced in the field of CF by Per Gustafsson.<sup>60</sup> With drugs that attack the basic CF defect, there was a resurgence of interest in biomarkers of *CFTR* function such as the sweat chloride, nasal potential difference measurement, and intestinal current measurements.<sup>61</sup> To better study the first steps in CF lung disease, the *in vivo* study of mucociliary clearance was also reengineered.<sup>62</sup>

## CENTRALIZED CARE BY MULTIDISCIPLINARY TEAMS FOR PATIENTS WITH CYSTIC FIBROSIS

### GUIDELINES AND CONSENSUS STRIVE FOR EVIDENCE-BASED CYSTIC FIBROSIS CARE

In many places, in 1989 the care for patients with CF was solely in the hands of a motivated clinician trying to do his best. But the insight to the basic defect boosted improvements in patient care. The importance of care in a CF center with appropriately staffed multidisciplinary teams was increasingly recognized and aspired to.<sup>63,64</sup> At present, optimal centralized CF care implies that all CF team members bring in their specific expertise (nurse, physiotherapist, social worker, psychologist, dietician, administrative support, and if possible pharmacist) for the full benefit of the patient.<sup>65</sup> All work under the coordination and with the support of the CF center director.

The results of several seminal trials led to a better evidence base for the treatment of CF lung disease. Treatment with rhDNase, inhaled tobramycin, and azithromycin became standard care. To align thoughts on optimal treatment strategies, several consensus documents were drafted by the CFF. Under the momentum of Gerd Doering (ECFS president from 1998 to 2006), a series of European consensus documents were prepared, discussed in beautiful Artimino, and published.<sup>65-70</sup> Equally successful consensus conferences were held at Lake Garda, organized by Carlo Castellani, with a focus on *CFTR* mutation analysis,<sup>71</sup> CF NBS,<sup>36</sup> and carrier screening.<sup>72</sup>

### POPULATION OF CYSTIC FIBROSIS PATIENTS CHANGES

The improved care was first noticeable in the pediatric population. Maintaining good nutrition and treating airway obstruction and infection intensively transformed not only how children with CF looked but also the atmosphere on the pediatric wards. The CF wards were a place where many children and adolescents repeatedly spent several weeks on end. They inevitably got to know each other and befriended and adored hanging out together. On many occasions, they even got themselves into mischievous behavior. The need for segregation according to type of bacterial infection hit this population like a bomb. But, over time, nearly every pediatric clinic saw a decrease in the number and duration of hospital admissions for children with CF. Sadly, many of the usual residents on the wards died. Some reached adult age with or without lung transplant. The newer generations of children with CF never needed this high number of hospital admissions. Increasingly, home intravenous antibiotic therapy became an alternative for in-hospital treatment. The importance of patient segregation was much better understood and accepted by newer generations of patients.

Good nutritional status and a normal median FEV<sub>1</sub> until adolescence was achieved, were reasonably satisfied with the early CF disease course. In addition, in an increasing number of countries NBS allowed optimal CF care from birth onward. But despite this optimal start, Australian researchers demonstrated that up to half of the patients already had bronchiectasis during preschool years.<sup>73</sup> Airway inflammation and infection start very early in life.<sup>74</sup> There is thus an obvious need for even better management of young children with CF.

More and more, CF was no longer a disease of mainly children and adolescents. The number of adults with CF increased steadily, with more patients surviving until adult age with or without lung transplant, as well as with new diagnoses of CF in adults. In many CF clinics, adults now equal or outnumber the children. Still, the mean age of expected survival (around 50 years) for current birth cohorts and the, at present, median age at death (around 30 years) are much below any nation's average. The increasing number of adults is so far not paralleled by the necessary number of physicians and facilities for adult CF care. In many clinics, a transition program to adult care is not available and pediatricians continue to treat adults with CF. Because this increase in adult patients is anticipated to continue,<sup>75</sup> training adult specialists in CF is a key action point that will be taken up by a joint ECFS and European Respiratory Society task force.

### LUNG TRANSPLANT BECOMES AN OPTION FOR END-STAGE LUNG DISEASE

Lung transplant, first performed in Stanford in 1981 and first applied in CF around the time the *CFTR* gene was discovered, became a valid option for patients with end-stage lung disease.<sup>76</sup> Techniques evolved from heart-lung transplant, double lung transplant, and sequential single lung transplant with clam shell incision to sequential single lung with isolated submammary incision, mostly without the need for cardiopulmonary bypass. The outcome after transplant is better for CF than for other indications. In the best centers, 10-year survival post lung transplant for patients with CF is up to 80%. Still, the availability of transplant services differs greatly between countries and despite an improved quality of life patients face new complications post transplant such as rejection, obliterative bronchiolitis, medication side effects, and malignancy, as well as needing to continue many CF medications from before transplantation.

### WE GAIN MAJOR NEW INSIGHTS INTO AIRWAY MICROBIOLOGY

Over time and with more patients attaining adult age, we gained major new insights into airway microbiology. In Europe, *Pseudomonas* lung infection had always been in the center of attention. Niels Hoiby and the Copenhagen

CF center were in the vanguard of this research. For years, there was a transatlantic disagreement about the importance of *Pseudomonas*: pro and con debates were regular features at CF meetings. But with increasing proof of patient–patient transmission and lung deterioration after *Pseudomonas* acquisition, the transatlantic dispute about the importance of *Pseudomonas* lung infection was finally settled. All eventually agreed that it is necessary to eradicate early *Pseudomonas* infection and to segregate patients with *Pseudomonas* lung infection from patients without *Pseudomonas* infection: this was the end of summer holiday camps, beginning of patient segregation, and start of excessive fear of water, with the hope of avoiding *Pseudomonas* infection.<sup>70</sup> As a result of eradication of early *Pseudomonas* infection, chronic *Pseudomonas* infection in children with CF has decreased from more than 50% to around 10%.<sup>77,78</sup>

The metabolism of *Pseudomonas* in patients with CF was better understood, especially the switch to the mucoid “biofilm mode” in the reduced oxygen concentrations in airway mucus.<sup>79</sup> New pathogens other than the well-known *Staphylococcus aureus* and *Pseudomonas aeruginosa* were described: *Burkholderia cenocepacia*, capable of suddenly decimating patients; members of an ever-growing group of closely related bacteria, *Stenotrophomonas maltophilia*; and more recently *Achromobacter xylosoxidans*. But clinicians also appreciated the importance of nontuberculous mycobacteria, with *Mycobacterium abscessus* being the most feared, and a growing list of fungi from the well-known *Aspergillus fumigatus* to the lesser known *Scedosporium apiospermum* and black yeast, *Exophiala dermatitidis*.<sup>80,81</sup>

Systematic study of the lung microbiota taught that even the normal lung is not sterile.<sup>82</sup> The lung microbiota in CF is infinitely complex with a very vast spectrum of potential pathogens including countless anaerobic bacteria.<sup>83</sup> With increasing patient illness, the diversity of lung microbiota decreases.<sup>84</sup> So, appropriately, CF treatment diversified in attention from mainly *S. aureus* and *P. aeruginosa* to any potential pathogen in the CF lung and the interactions between microorganisms, which may be adverse, beneficial, or neutral.

Because pulmonary exacerbations lead to lung function decline, definition, frequency, risk factors, and treatment were studied intensely.<sup>85–87</sup>

## CYSTIC FIBROSIS REGISTRIES BECOME EVEN MORE IMPORTANT TOOLS

As patients with CF become older, many CF-specific complications emerge or their prevalence is better appreciated. A few are named here: CF-related diabetes, kidney stones, osteoporosis, and intestinal malignancies.<sup>88–91</sup> Not only as outcome parameters in clinical trials, but, also in the clinic more attention went to patient well-being, especially in adults. The new research fields of pain and anxiety were opened.<sup>92,93</sup>

Although CF registries predate the discovery of the *CFTR* gene, there was a boost in exploring cross-sectional and longitudinal patient data for obvious health economic reasons,

to have robust data on the natural history of the disease and define priorities in research, to learn about CF-specific complications, to study outcome parameters, to understand the diversity and geographic distribution of *CFTR* mutations, and also for benchmarking and identification of best practice models by comparing outcome between centers to lead to quality improvement.<sup>94</sup>

## PARTNERING MOVED THE CYSTIC FIBROSIS FIELD FORWARD

More than before, academic groups joined forces. This was facilitated by the new means of communication available: e-mail, teleconferencing, websites, Skype, drop boxes, and “clouds.” Further, contacts between scientific as well as patient/parent CF organizations around the world have become closer.

In Europe, the increasing importance of CF research and care translated into a growth in the membership of the ECFS. The yearly ECFS meetings transformed from the gathering of CF “addicts” fitting in a small auditorium to a full-size conference with parallel sessions and well over 2000 attendees. The ECFS gained visibility via a website and via the foundation of the *Journal of Cystic Fibrosis* in 2001. During the leadership of Stuart Elborn, the activities of the ECFS expanded further. The ECFS-CTN was founded in 2008. The registry working group was transformed to the European Cystic Fibrosis Society Patient Registry in December 2010. Existing European working groups such as the Cystic Fibrosis Newborn Screening Group and the Diagnostic Network obtained better support, and several new working groups were formed (ECFS Exercise Working Group, ECFS Gene Modifier Working Group, ECFS Lung Microbiome Working Group, and ECFS Non-Tuberculous Mycobacteria Working Group).

Early on, the CFF had already taken the initiative of partnering with companies. Their initiative of supplying major research funding to companies boosted innovative drug development for CF. And this initiative was broadened: CF clinicians brought input into the clinical phase of drug development. Their background knowledge of CF and the clinical trial networks facilitated a more efficient clinical phase of drug development.

CF physicians came into closer contact with health authorities. Bringing new drugs with a favorable risk–benefit balance to the market requires careful evaluation. Here again, the background knowledge of CF physicians was increasingly appreciated to assist in the correct assessment. CF physicians familiarize themselves with the complex clinical trial directives and regulations. Discussions between CF clinicians, pharmaceutical company representatives, patients, and the European Medicines Agency all aim for more efficient and safe clinical research.

Patients and patient representatives became more assertive and became involved in several aspects of CF care and

research. Their vision on life changed from “hoping to survive” to “hoping to see the cure of CF.”

## ALL PARTIES ARE AWARE OF MAJOR CHALLENGES AHEAD

Although better treatments are available, they are continuously added to the existing ones so that the treatment burden becomes extremely high and is a risk factor for low treatment adherence.<sup>95</sup> Comparative effectiveness research initiated by academia becomes more and more important. This type of clinical trials should be facilitated by separate rules for “low intervention clinical trials” (e.g., a marketed drug with a good safety profile being tested off-label), a new category recently put forward in the new European Clinical Trial Regulation ([http://ec.europa.eu/health/files/clinicaltrials/2012\\_07\\_/proposal\\_en.pdf](http://ec.europa.eu/health/files/clinicaltrials/2012_07_/proposal_en.pdf)). Let us hope that the European funding organizations will empower this regulation with the necessary finances. The ever increasing number of adults with CF needs to be paralleled with the necessary number of adult-trained physicians.

In Europe, the gap in outcome between patients with CF in high- and low-income countries is large.<sup>96</sup> Lobbying for more financial support and better access to care in every country should be a priority.

Even in high-income countries, affordability of care should be preserved. The very high cost of new molecules is a concern, especially in the current economically challenging times. We cannot develop medicines that cannot be afforded by those who need them.<sup>97</sup>

### A SPECIAL HOMAGE TO CFF AND CFF-TDN

I discussed the change in the field of CF from 1989 until present from the perspective of the European CF clinician. But to put this entire period into the correct perspective, a specific mention of the importance of the work in North America is needed. From the discovery of the *CFTR* gene until the present time, many major new insights in CF were gained in the United States. Without the CFF, the field of CF would not be what it is today. The CFF was a major financier of not only research in the United States but also selected projects outside the United States. The visionary role of Bob Beall cannot be emphasized sufficiently. He was most likely the first to believe in the possibility of a cure for CF. He worked tirelessly toward that goal by facilitating CF research and promoting excellence in CF care. Bob Beall surrounded himself with equally brilliant people like Preston Campbell and Bruce Marshall. Together with excellent clinical researchers headed by Bonnie Ramsey, Bob Beall saw the importance of a specific clinical trial network dedicated to CF research. His and their example has inspired us all to give the best for patients with CF, be it in research or in clinical care.

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# 2

## Epidemiology of cystic fibrosis

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STEPHANIE J. MACNEILL

### INTRODUCTION

This chapter explores the epidemiology of cystic fibrosis (CF), including the influence of the different genotypes and mutation classes associated with the disease, its incidence and prevalence, patient survival, demographic and clinical characteristics, and factors influencing prognosis.

Describing the health of large patient populations is made possible in part through the use of national disease registries. As such, we have made use of the 2011 annual reports from the Cystic Fibrosis Foundation (CFF) in the United States,<sup>1</sup> Cystic Fibrosis Trust in the United Kingdom,<sup>2</sup> Cystic Fibrosis Canada,<sup>3</sup> and 2008–2009 data from the European CF Society.<sup>4</sup> We also included 2009 data from Australia published by Bell et al.<sup>5</sup> Comparisons between countries, however, should be made cautiously as countries will have different health-care systems and treatment practices and registries will differ in the way data are collected (annual reviews or encounter based, for example), levels of completeness, and reference values used for nutritional and pulmonary outcomes. Additionally, it is worth noting that registry studies—like all observational studies—are prone to ascertainment bias where all patients are not represented equally in the cohort. In relation to registry studies, this may stem from national screening practices (or lack thereof) where patients with certain genotypes are less likely to be identified. Registries based on being treated at specialist centers are also at risk of bias if there are groups of patients who are unable to access such services. This may be for reasons of geography or ability to pay, for example. Given this potential for bias, it is important when interpreting results to be mindful of how patients are identified for such registries and their estimated coverage. For example, the 2011 annual report produced by the Cystic Fibrosis Trust in the United Kingdom—where there exists a universal access health-care system and all CF patients are seen at specialist centers—included data on 89% of the patients registered at these centers. Data from Italy, however, which are included

in the European Cystic Fibrosis Society's report, cover only an estimated 14% of patients.

### BIRTH AND POPULATION PREVALENCE

#### BIRTH PREVALENCE

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The birth prevalence of CF in different populations is described in Table 2.1 and illustrates how CF varies greatly by region and population. It is most common in northern European and Caucasian North Americans and Ashkenazi Jews, although it has also been identified in Asia, South and Central America, and Africa. Within a country, differences are frequently observed reflecting the ethnic diversity of the population. In California, for example, researchers observed a birth prevalence of 1:5025 across all births, yet when split by ethnic group it varied from 1:2577 in Caucasians to only 1:5848 among African-Americans.<sup>6</sup> It should thus be emphasized that the old cliché of CF being purely a disease of white races can firmly be laid to rest.

Caution must be exerted, however, when making comparisons between countries and between studies. Identification of patients with CF will vary between studies, from the use of national patient registries with established neonatal screening to surveys at single centers. Also, the methods used for diagnosing patients with CF will vary over time and, in some cases, between countries.

Underdiagnosis in some countries can lead to underestimates in incidence. This may stem from limited availability of newborn screening or deaths prior to diagnosis. For example, when using data from national registries across Europe, McCormick et al.<sup>43</sup> observed that the size of the CF populations in non-EU countries was lower than in EU countries within Europe. While striking, the authors highlighted that this disparity may be due in part to underdiagnosis and higher rates of early infant mortality in these countries and therefore urged caution in the interpretation of these results.

Table 2.1 Birth prevalence of CF by country and population<sup>a</sup>

Population	Incidence	Details
Africa		
South Africa—black population [7]	784 to 13,924	Predicted based on carrier frequency
South Africa—Cape Town [8]		Based on the number of new patients and live births during a 4-year period at a children's hospital
White population	2,000	
Black population	12,000	
Asia		
Japan [9]	350,000	Based on reported cases and live births after 1980
Australia		
Australia [5]	2,986	Registry study using data averaged over 5 years to 2008
Australia—Victoria [10]	3,139	Based on live births in Victoria between 1989 and 2008
New Zealand (non-Maori) [11]	3,179	Based on data collected between 1960 and 1983
Europe		
Austria [12]	3,500	Review of studies using survey or registry data
Austria [13]	3,436	Review of newborn screening program in 2004
Belgium [12]	2,850	Review of studies using survey or registry data
Belgium—Wallonia [13]	7,509	Review of newborn screening program in 2004
Bulgaria [12]	2,500	Review of studies using survey or registry data
Cyprus [12]	7,914	Review of studies using survey or registry data
Czech Republic [12]	2,833	Review of studies using survey or registry data
Czech Republic—Western region [14]	9,100	Study of newborn screening programs between 2004 and 2005
Denmark [12]	4,700	Review of studies using survey or registry data
Denmark [15]	4,760	Based on data between 1945 and 1985
Denmark—Faroe Islands [16]	1,775	Based on data between 1954 and 1993
Estonia [12]	4,500	Review of studies using survey or registry data
Finland [12]	25,000	Review of studies using survey or registry data
France [12]	4,700	Review of studies using survey or registry data
France [13]	1:4,384	Review of newborn screening program in 2004
France—Brittany [17] <sup>b</sup>	3,268	Analysis of births in Brittany 2009
Germany [12]	3,300	Review of studies using survey or registry data
Germany [13]	2,291	Review of newborn screening program in 2004
Greece [12]	3,500	Review of studies using survey or registry data
Ireland [12,18]	1,353	Review of studies using survey or registry data
Ireland [19]	1,838	Using national registry data and national health statistics
Italy [12,20]	4,238	Review of studies using survey or registry data
Italy [13]	4,618	Review of newborn screening program in 2004
Italy—regions [14]	2,650 to 5,200	Study of regional newborn screening programs between 2004 and 2005
Italy—Veneto/Trentino Alto-Adige [21]	3,540	Study of births between 1990 and 2005
Netherlands [12,22]	4,750	Review of studies using survey or registry data
Netherlands [23]	6,062	Study comparing two screening strategies between 2008 and 2009
Norway [24]	6,574	Study of screening program between 1982 and 1984
Poland [12]	5,000	Review of studies using survey or registry data
Portugal [12]	6,000	Review of studies using survey or registry data
Romania [12]	2,056	Review of studies using survey or registry data
Slovakia [12]	1,800	Review of studies using survey or registry data
Slovenia [12]	3,000	Review of studies using survey or registry data
Spain [12]	3,750	Review of studies using survey or registry data
Spain [13]	2,840	Review of newborn screening program in 2004

(Continued)

Table 2.1 (Continued) Birth prevalence of CF by country and population<sup>a</sup>

Population	Incidence	Details
Spain—regions [14]	4,000 to 10,500	Study of regional newborn screening programs between 2004 and 2005
Sweden [12,25]	5,600	Review of registry studies
Russia [13]	3,714	Review of newborn screening program in 2004
United Kingdom [26]	2,381	Analysis of national survey data and death certificates between 1968 and 1987
United Kingdom [27]	2,415	Average proportion of CF births between 1968 and 1987
United Kingdom—regions [14]	2,250 to 2,850	Study of regional newborn screening programs between 2004 and 2005
United Kingdom—East Anglia [28]	3,245	Data from neonatal screening in 1990
United Kingdom—Wales [13]	1,888	Assessment of newborn screening program in 2004
United Kingdom—Northern Ireland [29]	1,969	Based on identified cases and live births between 1961 and 1971
United Kingdom—Northern Ireland [30]	1,807	Assessment of newborn screening program between 1983 and 1987
United Kingdom—Scotland [13]	2,874	Assessment of newborn screening program in 2004
United Kingdom—Scotland [31]	1,984	Calculated from heterozygote frequencies in a cohort of women attending antenatal screening
Middle East		
Bahrain [32]	5,800	Based on diagnoses and population statistics
Israel: Ashkenazi Jews and Arabs [33]	1,800 to 4,000	Based on identified cases in Israel between 1946 and 1975
Jordan [34]	2,560	Based on newborn screening statistics
United Arab Emirates [35]	15,000	
North America		
Canada [36] 1971–1987	2,714	Based on a study of temporal trends in CF birth prevalences
2000	3,608	
Canada—Saguenay-Lac-St.-Jean (Quebec) [37] <sup>c</sup>	902	Based on data between 1975 and 1988
United States [38]		Using national registry data between 1989 and 1991 and statistical models to account for underdiagnosis due to death prior to diagnosis
Whites	3,419	
Non-whites	12,163	
United States—California [6]	5,025	Using data from state-wide newborn screening program
United States—Massachusetts [39]	2,908	Using data from newborn screening between 1999 and 2003
United States—Michigan [40]	3,198	Using data from newborn screening program between 2007 and 2008
United States—Wisconsin [30]	3,983	Using data from newborn screening program between 1994 and 2002
South America		
Brazil [41]	6,902	Based on known cases and population samples

Source: Daigneault J et al., *Hum Biol*, 64(1), 115–9, 1992.

<sup>a</sup> Expressed as the number of live births per incident case of CF.

<sup>b</sup> A number of studies have been conducted in Brittany studying its relatively high birth prevalence over time. Earlier studies have shown slightly higher birth rates [21,42] than that presented here for Brittany.

<sup>c</sup> The high prevalence in Saguenay-Lac St. Jean is thought to be due to founder effect and genetic drift.

## TEMPORAL TRENDS IN INCIDENCE

Since the discovery of the CF gene, carrier testing has become possible and there has been some interest in assessing whether there have been subsequent changes in the birth prevalence of CF due, in part, to families choosing

not to have children on learning of their carrier status. In northeastern Italy, a decrease in the birth prevalence of CF was observed between 1993 and 2007, which was greater in the eastern region where carrier testing is more widely available.<sup>44</sup> In Canada, the CF birth prevalence was stable between 1971 and 1987 and then from 1988—a year prior to

the advent of carrier screening—there was a linear decline in birth prevalence until 2000.<sup>36</sup> In Victoria, Australia, researchers noted a decline in the live-birth prevalence of CF after the implementation of newborn screening,<sup>45</sup> and in Massachusetts researchers observed fewer children than expected identified with CF through newborn screening in 2003 through to 2006.<sup>46</sup> It was suggested that the provision of preconception and prenatal screening to the general population to identify carriers of CF might result in a decrease in the number of births of children with CF.<sup>46</sup>

In Brittany, France, where CF is relatively common (1:2948)<sup>42</sup> researchers noted a 30.5% difference in the 10-year birth prevalence (1992–2001) of CF depending on whether CF-affected pregnancies that were terminated during pregnancy were included.<sup>47</sup> The researchers concluded that prenatal diagnoses were responsible for this decrease. The region noted a 40% decline in incidence over a 35-year period until 2009.<sup>17</sup> Specifically, they noted a breakpoint in the late 1980s when prenatal diagnoses became more common after which the incident rate remained relatively stable.

## POPULATION PREVALENCE

Population prevalence statistics are rarely presented in the literature, but they can be calculated with the use of specialist patient registries and official population statistics. These will still be influenced by the estimated coverage of the patient registries, however, which can vary greatly between countries. The 2008–2009 annual report for the European Cystic Fibrosis Society Patient Registry noted a wide variation in the estimated coverage of the data provided,<sup>4</sup> and many national registries noted coverage ranging from 14% to 100%. A summary is presented in Table 2.2 illustrating a wide variation in estimated prevalence across countries. CF was most common in Ireland and least common in Romania, Finland, and the Baltic countries of Latvia and Lithuania.

Farrell et al.<sup>12</sup> produced an extensive report of population prevalences for European countries using survey data and registry information. Combining data from all 27 EU countries, they estimated a population prevalence of 7.37 per 100,000 in 2004, which is only slightly lower than the 2011 prevalence in the United States, as described earlier.

Despite reductions in the birth prevalence of CF noted in some countries, there is evidence that the population prevalence is increasing. Since 2007, the number of new diagnoses in the United Kingdom exceeded the number of deaths by approximately 145 each year, suggesting an increase in prevalence of 0.2 per 100,000 population per year.<sup>2</sup> Similar trends emerge from US data from 2006.<sup>2</sup>

## GENOTYPE DISTRIBUTION

An extensive international analysis by the Cystic Fibrosis Genetic Analysis Consortium published in 1995 described the distribution of *CFTR* genotypes and observed that

the most commonly observed CF mutations were *F508del* (66.0%), followed by *G542X* (2.4%), *G551D* (1.6%), *N1303K* (1.3%), and *W1282X* (1.2%).<sup>54</sup>

Whereas *F508del* proved to be common, striking between- and within-country differences have been observed. Bobadilla et al.<sup>55</sup> conducted an international review of published genotype prevalences that illustrates this. Within Europe *F508del* was the most common, yet its prevalence varied from 87.5% in Denmark to only 31.0% in Lithuania. Within France, United Kingdom, and Italy, there are noted geographic differences. Ethnic differences were noted in the United Kingdom, where the prevalence of *F508del* mutation was only 19.2% in a Pakistani subpopulation compared to 75.3% across the country as a whole. In Africa and the Middle East, other mutations such as *W1282X* and *S549R* were most common among Ashkenazi Jews and in the United Arab Emirates, respectively. In other countries in this region, *F508del* remained the most common mutation but was less common than in Europe (17.6% in Tunisia, for example, compared with 75.3% in the United Kingdom). In South America, the prevalence of *F508del* varied from 25.0% in Ecuador to 58.6% in Argentina. In North America, there were clear within-country differences: in Lac St. Jean, Quebec, the prevalence of *F508del* was 59.0% compared to 71.4% in nearby Quebec City. In the United States the prevalence across the country was 68.6%, whereas it was only 48.0% among African-Americans.

It has been observed that some non-*F508del* mutations are more common in particular populations—*G542X* is seen more commonly in Mediterranean Europe and Africa; *G551D* in those of Celtic descent in Ireland, United Kingdom, and Brittany; *W1282X* in Ashkenazi Jews; *394delTT* in countries bordering the Baltic Sea; *3120+IG->T* in African-Americans; *621+IG->T* in Lac St. Jean; *R1162X* in US Native Americans; and *3849+10KbC->T* in US Hispanics.<sup>55</sup> The implication of this variation is that in heterogeneous populations screening for a wide array of genotypes is important. Furthermore, this has implications for health economics; a greater cost burden for expensive new molecules such as ivacaftor will fall on countries with a high prevalence of the *G551D* mutation.

With the discovery of the *CFTR* gene and subsequent delineation of the various mutations, there have been efforts to determine whether specific mutations—or functional classes—are associated with improved or worse outcomes. Although considerable variability within functional classes exists, some common trends have emerged. McKone et al.<sup>56</sup> observed lower mortality in patients with functional classes IV and V compared to those with homozygous *F508del*. When comparing classes I–III with IV and V, they observed a reduced mortality in the latter, which was not explained by forced expiratory volume in 1 second (FEV<sub>1</sub>), body mass index (BMI), pseudomonas infection, or pancreatic sufficiency.<sup>57</sup> Similarly, de Garcia et al.<sup>58</sup> observed lower baseline spirometry and greater loss of lung function over follow-up in adults with *CFTR* mutation classes I or II on both chromosomes, and Koch<sup>59</sup> noted that a class IV *CFTR* mutation appeared to offer some protection against pancreatic insufficiency.

Table 2.2 Population prevalence of cystic fibrosis

Population	Population prevalence (per 100,000)	Year	Details
Australia			
Australia	14.07	2011	Based on the 2011 Australian CF registry annual report and official population statistics [48,49]
Europe			
Austria [12]	8.39	2004	Review of studies using survey or registry data
Belgium [12]	10.3	2004	Review of studies using survey or registry data
Belgium <sup>a</sup>	11.05	2009	Based on the 2008–2009 European Cystic Fibrosis Society Patient Registry Report and official population statistics [4,50]
Bulgaria [12]	2.26	2004	Review of studies using survey or registry data
Cyprus [12]	3.35	2004	Review of studies using survey or registry data
Czech Republic [12]	5.56	2004	Review of studies using survey or registry data
Czech Republic <sup>a</sup>	4.86	2009	Based on the 2008–2009 European Cystic Fibrosis Society Patient Registry Report and official population statistics [4,50]
Denmark [12]	7.61	2004	Review of studies using survey or registry data
Denmark <sup>a</sup>	8.18	2009	Based on the 2008–2009 European Cystic Fibrosis Society Patient Registry Report and official population statistics [4,50]
Estonia [12]	6.18	2004	Review of studies using survey or registry data
Finland [12]	1.23	2004	Review of studies using survey or registry data
France [12]	7.50	2004	Review of studies using survey or registry data
France <sup>a</sup>	9.74	2009	Based on the 2008–2009 European Cystic Fibrosis Society Patient Registry Report and official population statistics [4,50]
Germany [12]	8.29	2004	Review of studies using survey or registry data
Germany <sup>a</sup>	6.84	2008	Based on the 2008–2009 European Cystic Fibrosis Society Patient Registry Report and official population statistics [4,50]
Greece [12]	5.21	2004	Review of studies using survey or registry data
Hungary [12]	4.09	2004	Review of studies using survey or registry data
Hungary <sup>a</sup>	6.15	2009	Based on the 2008–2009 European Cystic Fibrosis Society Patient Registry Report and official population statistics [4,50]
Ireland [12]	29.8	2004	Review of studies using survey or registry data
Ireland <sup>a</sup>	25.78	2008	Based on the 2008–2009 European Cystic Fibrosis Society Patient Registry Report and official population statistics [4,50]
Italy [12]	8.72	2004	Review of studies using survey or registry data
Latvia [12]	1.04	2004	Review of studies using survey or registry data
Lithuania [12]	1.30	2004	Review of studies using survey or registry data
Luxembourg [12]	4.31	2004	Review of studies using survey or registry data
Malta [12]	5.79	2004	Review of studies using survey or registry data
Netherlands [12]	7.81	2004	Review of studies using survey or registry data
Netherlands	7.81	2009	Based on the 2008–2009 European Cystic Fibrosis Society Patient Registry Report and official population statistics [4,50]
Poland [12]	2.56	2004	Review of studies using survey or registry data
Portugal [12]	2.71	2004	Review of studies using survey or registry data
Romania [12]	1.06	2004	Review of studies using survey or registry data
Slovakia [12]	6.27	2004	Review of studies using survey or registry data
Slovenia [12]	3.28	2004	Review of studies using survey or registry data
Spain [12]	5.46	2004	Review of studies using survey or registry data
Sweden [12]	4.03	2004	Review of studies using survey or registry data
Sweden <sup>a</sup>	7.18	2009	Based on the 2008–2009 European Cystic Fibrosis Society Patient Registry Report and official population statistics [4,50]

Table 2.2 (Continued) Population prevalence of cystic fibrosis

Population	Population prevalence (per 100,000)	Year	Details
United Kingdom [12]	13.7	2004	Review of studies using survey or registry data
United Kingdom	15.47	2011	Based on the number of patients registered in the 2011 CF Trust Registry annual report and official population statistics [2,50]
Middle East			
Israel	7.91	2009	Based on the 2008–2009 European Cystic Fibrosis Society Patient Registry Report and official population statistics [4,51]
North America			
Canada	11.7	2011	Based on the 2011 Canadian Cystic Fibrosis Registry annual report and 2011 census data [3,52]
United States	8.7	2011	Based on the 2011 CF Foundation Registry annual report and estimated population size for 2011 [1,53]

<sup>a</sup> Where the population prevalence was estimated using data from the European Cystic Fibrosis Patient Registry report, the number of patients with CF was estimated from the number of patients seen that year and estimated registry coverage that year.

## SURVIVAL

As in any life-threatening disease, much research has been conducted to understand patient survival—estimating current survival, temporal trends, and predictors. The way in which survival is measured, however, is varied as described later. The many factors influencing survival are discussed in the prognosis section of this chapter.

## MORTALITY

Crude mortality rates for CF are often presented as the number of deaths per 1000 (or 100,000) population. In the general population, CF as a cause of death is rare—the crude CF mortality rate in the general population in 2012 was 0.16 per 100,000 in England and Wales.<sup>50,60</sup> Among young people aged 5–24 years, however, it represents 1.3% of all deaths.

When estimating the mortality rate in CF patients, it is important that reliable data on the size of the affected population are used and a complete ascertainment of deaths is available. National registries provide useful data in this respect. Using 2011 national registry data, the mortality rate among CF patients in the United States was measured at 16 per 1000 registered patients<sup>1</sup> and 12 per 1000 in the United Kingdom<sup>2</sup> and in Canada.<sup>3</sup>

Using a relatively new patient registry in France, researchers noted an improvement in the crude death rate from 21.6 per 1000 in 1994–1996 to 15.8 per 1000 in 2001–2003.<sup>61</sup> While not doubting these results, the researchers themselves highlighted that it was likely their registry was incomplete as they estimated that they only had 63% coverage of the total CF population assuming an incident rate of 1:4600.

Despite the flaws of the data used in the previous calculation, others have also noted a reduction in the CF mortality

rate. In England and Wales, Panickar<sup>62</sup> noted that mortality rates in children declined between 1968 and 2000 and that the biggest change was in deaths among infants under the age of 1 year, probably at least in part a result of better surgical management of meconium ileus. Separately, Lewis<sup>63</sup> noted that once patients reached 20 years there was little difference in mortality rates when looking at 3-year cohorts of patients between 1947 and 1967.

## MEDIAN AGE AT DEATH

Median age at death is a simple description of the ages of all patients who have died of CF. The calculation only uses data from those patients who have died and is not influenced by the current ages of those patients still living. As such, it is generally lower than the median survival (described in the section “Current Survival”) as survivors are not included. It is dependent on the completeness of the data available, and in patient registries the issue of completeness relates to how well the registry captures the full patient population and therefore all deaths in that population. When using routinely collected death data, the completeness of the data relates to the coding of deaths and ensuring that non-CF deaths in CF patients are captured. It is also worth noting that median age at death in small populations can be unstable and therefore comparisons with other larger populations or over time must be performed with caution.

Mindful of these caveats, there have been significant increases in the median age at death in the last decades. In England and Wales, the median age at death increased from 0–4 years in 1959 to 25–29 years in 2008.<sup>64</sup> In Spain, the median age at death increased from 4.4 years in males and 3.8 years in females in 1981 to 20.1 years and 17.7 years in males and females, respectively, in 2004.<sup>65</sup> In Australia, the mean age at death increased from 13.3 years in 1979 to 26.6 years in 2005.<sup>66</sup>

Using the most up-to-date available national registry data, the median age at death was reported to be 27.1 years in the United States,<sup>1</sup> 26.0 years in the United Kingdom,<sup>2</sup> 34.0 years in Canada,<sup>3</sup> and 25.0 years across Europe.<sup>4</sup>

## CURRENT SURVIVAL

Current survival is calculated based on age-specific mortality rates observed over a year and estimates life expectancy for a hypothetical population assuming that the current mortality rates reflect future rates and remain constant over time.<sup>67</sup> Current survival has been estimated to be 37.7 years in Italy<sup>68</sup> and 50.6 for males and 43.2 years in females in Canada.<sup>3</sup> In the United States and United Kingdom, who use similar methodology to estimate current survival, 2011 estimates of survival were 36.8 years in the former<sup>1</sup> and 41.5 years in the latter.<sup>2</sup>

## COHORT SURVIVAL

Cohort survival is similar to current survival, but it is calculated for different birth cohorts of patients. The technical complexities of calculating current survival in smaller populations have been described by Jackson et al.,<sup>69</sup> who illustrated the effectiveness of a parametric model to estimate survival. Using this method to predict survival beyond the observed data, they estimated median survival in the United States and Ireland in two birth cohorts: patients born between 1980–1984 and 1985–1994. Their analyses showed an improvement between the two cohorts with improved survival in the latter. For patients born between 1980 and 1984, survival was estimated at 37.8 years in males and 31.5 years in females in the United States and 32.2 years and 24.7 years, respectively, in Ireland. In

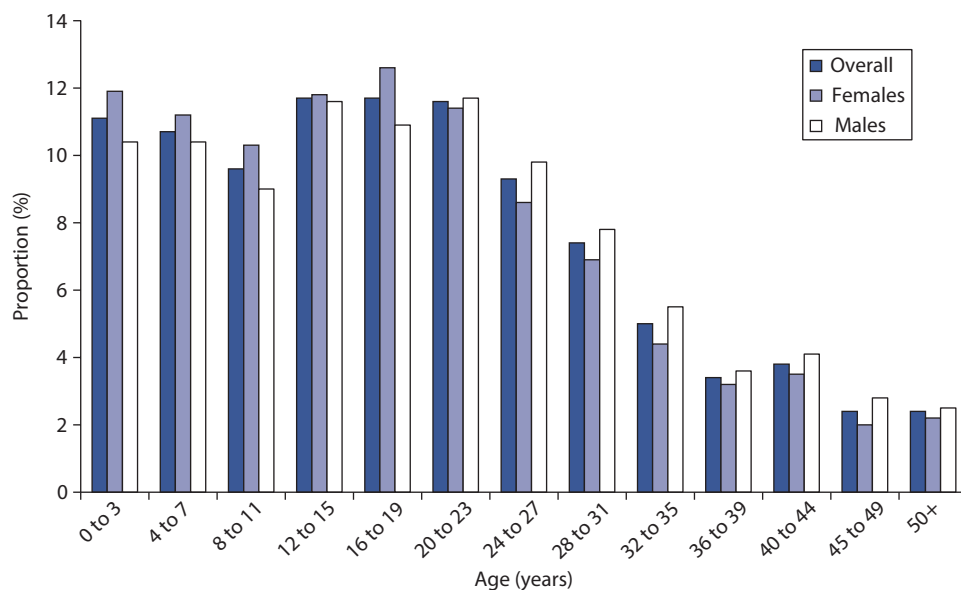
those born between 1985 and 1994, survival was estimated at 50.9 years in males and 42.4 years in females in the United States and 51.1 years and 39.0 years, respectively, in Ireland.<sup>70</sup> A separate study in the United Kingdom also noted improvements with successive birth cohorts when studying 3-year cohorts between 1968 and 1994.<sup>26</sup>

Being able to provide patients and their families with meaningful estimates of survival is important. Dodge<sup>26</sup> estimated that a male born in 2003 in the United Kingdom could expect to live to 42.6 years and a female to 36.9 years assuming that current age-specific mortality rates continue. Given that the researchers noted improvements, however, they suggest that it is not unrealistic to assume that median survival can surpass 50 years for patients born in 2000.

## AGE DISTRIBUTION

The current CF patient population is split almost evenly between adults and children: 48.3% of CF patients in the United States<sup>1</sup> are 18 years of age and older compared to 49% in Australia,<sup>5</sup> 57.2% in Canada,<sup>3</sup> and 48% across Europe.<sup>4</sup> The median age of patients seen in 2011 in the United Kingdom was 18 years, and the full distribution is presented in Figure 2.1.

This distribution is in stark contrast to the population profile in the United States in 1990, where 31.7% were younger than 15 years and only 7.3% were older than 30 years.<sup>71</sup> The care of CF patients has evolved greatly with the development of specialized adult care, which takes into account their unique needs. Given that patients are surviving longer and that the number of new diagnoses of CF exceeds the number of deaths, the need for specialist adult CF care will only grow.



**Figure 2.1** Age distribution of patients with cystic fibrosis seen at specialist centers in the United Kingdom in 2011. (From CF Trust, *Cystic Fibrosis Trust Annual Data Report 2011, 2013*.)

## LONG-TERM SURVIVORS

As survival in CF has improved, an interest in studying those patients surviving to 40 years has developed—an arbitrary cutoff, yet one that has been adopted in a number of studies<sup>72,73</sup> (see Chapter 25). In 2011, 8.6% of patients seen in the United Kingdom were 40 years and older.<sup>2</sup> Studying a cohort of these long-term survivors at a specialist adult clinic in the United Kingdom,<sup>74</sup> researchers noted that although these patients were less likely to be pancreatic insufficient and less likely to be homozygous *F508del* over three-quarters had at least one *F508del* allele. This suggests that these patients are not hugely dissimilar genetically from the rest of the CF population. On average, their lung function and BMI were well preserved and many were married and working, suggesting that the disease burden in these survivors is not as high as feared. Identifying predictors of long-term survival, however, has proved to be difficult and in a case-control study at the same UK clinic researchers only identified measures of good health at the time of transition to adult care as predictors.<sup>72</sup>

## CHARACTERISTICS AT PRESENTATION

CF is often diagnosed by the presence of clinical signs and symptoms—including those of chronic sinopulmonary disease, gastrointestinal or nutritional anomalies, salt loss syndromes, or genital abnormalities—and then corroborated

with laboratory results.<sup>75</sup> Newborn screening has become more widespread, and as such many patients are diagnosed prior to the development of these typical presentations.

## AGE AT DIAGNOSIS

When examining recent cohorts of patients with CF, it was noted that most are diagnosed within the first year of life: the median ages at diagnosis of patients in 2011 were 5 months in the United States,<sup>1</sup> 7 months in Canada,<sup>3</sup> and 3 months in the United Kingdom.<sup>2</sup> In a survey of European countries in 2008–2009, the median age was 6 months, but this varied between contributing countries from 1.9 months in Italy to 1 year in Latvia and Portugal.<sup>4</sup> The presence or absence of newborn screening influences these figures. The distribution of age at diagnosis in the United Kingdom is presented in Figure 2.2.

## NEONATAL SCREENING

Neonatal screening in CF typically begins with screening for high immunoreactive trypsinogen levels in the blood. High levels are then confirmed with a second test or DNA screening and then sweat chloride tests.<sup>75</sup> Protocols vary and are discussed in detail in Chapter 11. The proportion of current patients identified by newborn screening varies by country as newborn screening is not universally available. In 2009, 83% of new diagnoses in Australia were by newborn screening,<sup>5</sup> whereas in the United States this figure

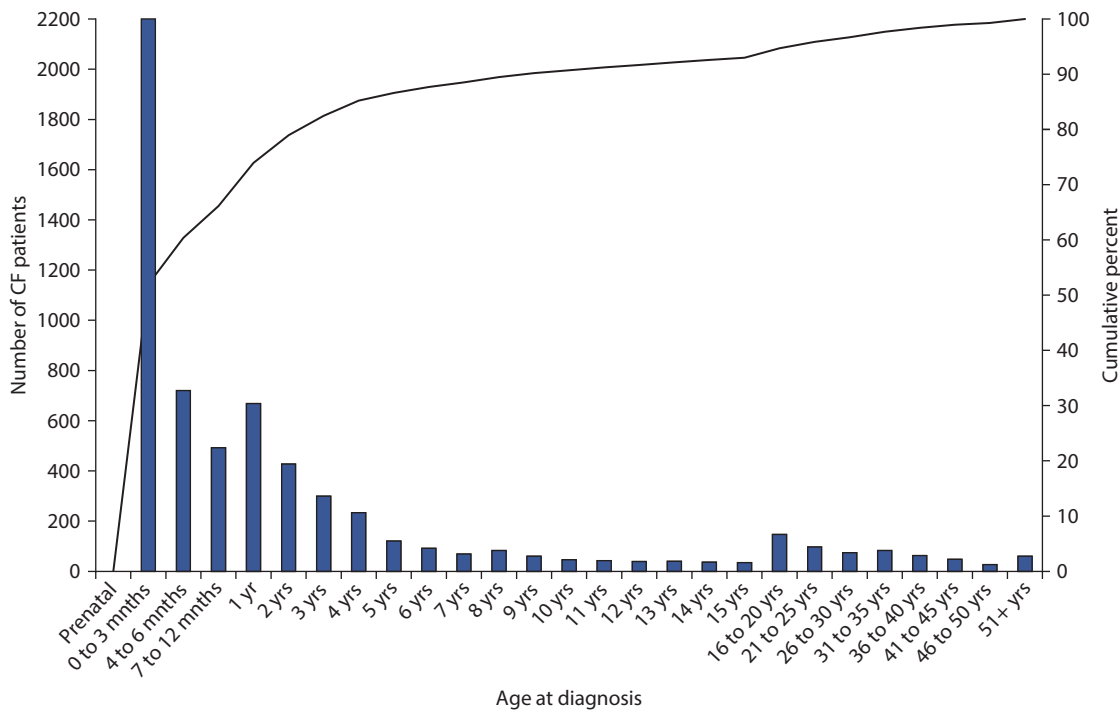


Figure 2.2 Distribution of age at diagnosis of patients seen in the United Kingdom in 2011 (including those diagnosed in 2011 and earlier). (From CF Trust, *Cystic Fibrosis Trust Annual Data Report 2011, 2013.*)

was 59%.<sup>1</sup> In a cross-sectional study of data from registries and specialist centers across Europe in 2008–2009, it was observed that 45% of children 5 years and younger were identified in newborn screening.<sup>4</sup> This figure, however, is skewed by the fact that newborn screening is not available in all contributing countries; thus, figures are likely to increase as access to newborn screening becomes more widespread.

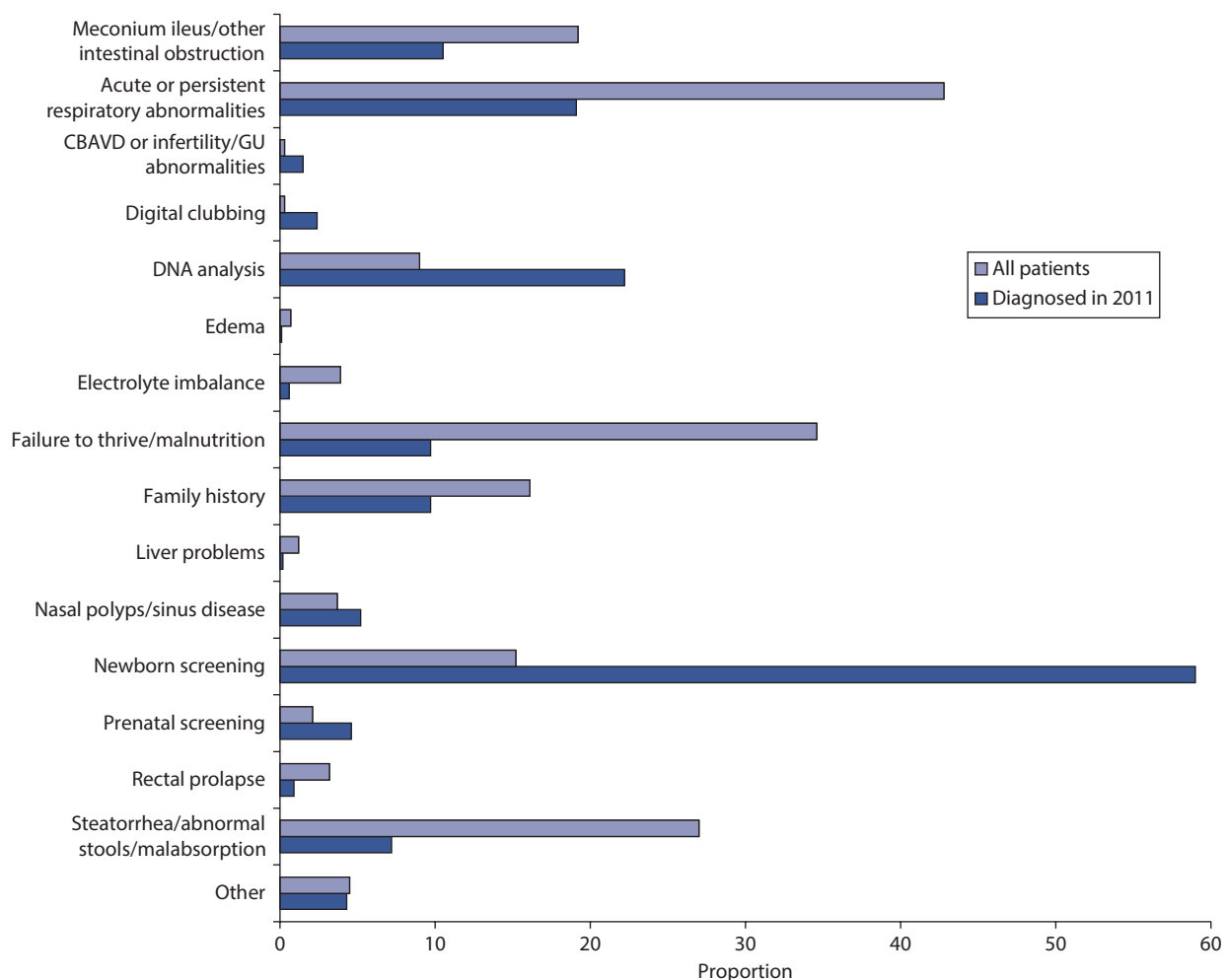
## ADULT PRESENTATIONS

Although most patients are diagnosed with CF in childhood, there is a growing proportion of patients who are first diagnosed as adults.<sup>76,77</sup> Although it is possible that, in some cases, the reasons for the delay in diagnosis may be a lack of access to specialist care, it has also been shown that patients diagnosed as adults have a different clinical presentation. They are less likely to present with typical gastrointestinal complications and are more likely to present with

respiratory disease,<sup>76,77</sup> being more likely to be pancreatic sufficient.<sup>76–79</sup> Sweat chloride levels in these patients also tended to be lower<sup>76,77</sup> and, while the presence of an *F508del* genotype was common, patients diagnosed as adults were less likely to be homozygote *F508del*.<sup>76–79</sup> A number of the non-*F508del* mutations more common in patients diagnosed as adults were classes IV to V.<sup>76,78</sup>

## MODE OF PRESENTATION

The US Cystic Foundation (CFF) Registry routinely reports statistics on the clinical characteristics patients present at the time of diagnosis. In patients diagnosed in 2011, most were identified by newborn screening, DNA analysis, and respiratory abnormalities.<sup>1</sup> When taking into consideration the rest of the current patient population, a large proportion presented with malnutrition, malabsorption, or respiratory abnormalities, as illustrated in Figure 2.3.



**Figure 2.3** Clinical characteristics at diagnosis in all patients seen in 2011 and those diagnosed in 2011. Characteristics are not mutually exclusive and, as such, proportions do not add to 100. (From CF Foundation, Patient Registry 2011: Annual data report to the centre directors, 2012.)

## CLINICAL FEATURES

### LUNG FUNCTION

Lung function is routinely measured in CF patients from the age of 6 years, the earliest age at which such clinical measures are likely to be reliable. (Although in specialist research centers, lung function is measured at younger ages.) In 2011, the median FEV<sub>1</sub> (percentage predicted) was 74.7% for patients 6 years and older in the United Kingdom<sup>2</sup> and in the United States the mean was 77.1%.<sup>1</sup> In Canada and Australia, where these measures are summarized separately for adults and children, the median for children of 6–17 years was 91.7% in Canada<sup>3</sup> and 92.8% in Australia (2009).<sup>5</sup> For adults, these values were lower, 64.6% in Canada and 66.4% in Australia. This decline in FEV<sub>1</sub> with age was also seen in the United States<sup>1</sup> and is illustrated in Figure 2.4 using data from the UK registry. While this decline in FEV<sub>1</sub> with age is well documented, there is evidence to suggest that FEV<sub>1</sub> levels have improved over time. The US CFF presented a cross-sectional analysis of national data in 1991, 2001, and 2011 comparing median FEV<sub>1</sub> by age and found that while the decline with age was consistent in each period median FEV<sub>1</sub> values were higher in 2011 than in previous years. They also noted improvements in FEV<sub>1</sub> across successive birth cohorts.<sup>1</sup>

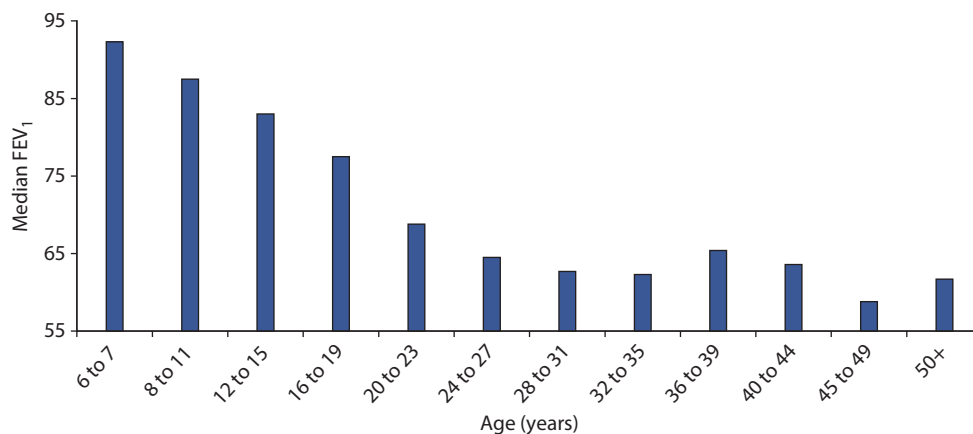
How lung function changes over time has been studied by a number of researchers, and recent work using large registry databases has provided useful information for clinicians. Taylor Robinson et al.<sup>80</sup> used longitudinal data from the Danish CF registry where monthly measures of FEV<sub>1</sub> on all patients (1969–2010) showed that a change in FEV<sub>1</sub> % predicted of more than 13% likely represents disease progression, whereas smaller changes are likely short-term fluctuations that patients may recover from. In this work, the authors also demonstrated that baseline FEV<sub>1</sub> % is a good predictor of future FEV<sub>1</sub> % up to 15 years later, although its predictive power decreases with time. *Pseudomonas aeruginosa* infection and pancreatic insufficiency were both associated with faster rates of decline in FEV<sub>1</sub>, and there was a clear

difference in baseline and rate of decline by birth cohort with improved baseline lung function in later cohorts. Similar findings were observed in North America by Konstan et al.<sup>81</sup> using data from the Epidemiologic Study of Cystic Fibrosis (ESCF) ( $n = 24,863$ ). They observed a number of factors that were associated with lung function decline in different age groups, but only three were significant across each age group: sex, the presence of crackles, and a higher baseline FEV<sub>1</sub>. Interestingly, the observed effect of sex on lung function decline was not the same across all age groups. In 6- to 8-year-olds females had a higher rate of decline, whereas in 9- to 17-year-olds females had a lower rate of decline.

The age of transition from pediatric to adult care is variable, but it usually occurs between the ages of 16 and 18 years and there is concern in the clinical community that there is a deterioration in health after this critical stage. Using data from the ESCF, Vanden Branden et al.<sup>82</sup> observed that the rate of decline in FEV<sub>1</sub> in adolescence (14–17.4 years) is less than that in young adulthood (18.5–22 years).<sup>82</sup> Patients at a greater risk of decline include those who have had a slower rate of FEV<sub>1</sub> decline in adolescence, have greater FEV<sub>1</sub> variability, have greater BMI decline, are male, have chronic use of inhaled antibiotics, have *Haemophilus influenzae*, do not have multi-drug-resistant *P. aeruginosa*, and have lower than expected FEV<sub>1</sub> and BMI at 18. Cross-sectionally, there is some evidence that patients are reaching adulthood in better health. The CFF explored how the proportion of 18-year-olds with normal or mild, moderate, or severe obstruction varied over different birth cohorts<sup>1</sup> (Table 2.3). They noted that in 2011 most 18-year-olds reached adulthood with normal lung function or only mild obstruction, a large improvement compared to 1986 when the proportion was less than a third. Also of note was that in 2011 only 6.1% had severe obstruction compared to 29.2% in 1986.

### GROWTH AND NUTRITION

The growth and nutrition of children with CF is usually measured in terms of height, weight, and BMI percentiles with appropriate reference populations. In the United States

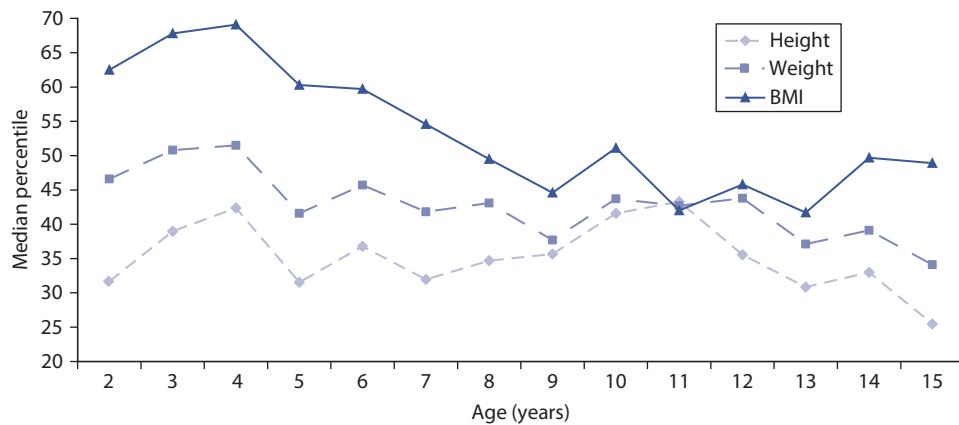


**Figure 2.4** Median forced expiratory volume in 1 second percentage (FEV<sub>1</sub> %) predicted by age group. Note that the zero is suppressed. (From CF Trust, *Cystic Fibrosis Trust Annual Data Report 2011, 2013.*)

**Table 2.3** Lung function distribution in 18-year-olds in 1986 and 2011

	18-Year-olds in 1986	18-Year-olds in 2011
Normal/mild obstruction ( $FEV_1 \geq 70\%$ )	31.9%	68.6%
Moderate obstruction ( $40\% \leq FEV_1 \leq 69\%$ )	38.9%	25.3%
Severe obstruction ( $FEV_1 < 40\%$ )	29.2%	6.1%

Source: CF Foundation, Patient Registry 2011: Annual data report to the centre directors, 2012.



**Figure 2.5** Median height, weight, and body mass index percentiles by age. (From CF Trust, *Cystic Fibrosis Trust Annual Data Report 2011, 2013.*)

and United Kingdom, national registry data showed that these measures tended to increase with age only up to 4 to 5 years and then decrease.<sup>1,2</sup> This is illustrated in the United Kingdom in Figure 2.5.

When summarized across ages, median height and weight percentiles in UK children (2–15 years) in 2011 were 34.8 and 42.9, respectively.<sup>2</sup> The median BMI percentile in this age band was 53.6 in the United Kingdom, 51.9 in the United States (2–19 years), and 44.4 in Canada (2–17 years).<sup>3</sup> The US CFF examined weight and height percentiles in successive cohorts by age and observed a trend toward small improvements in these measures across successive birth cohorts.<sup>1</sup>

Nutritional status in adults is generally measured by BMI, and median levels across national registries are broadly similar despite using slightly different age ranges: 22.0 in the United States,<sup>1</sup> 22.1 in Canada,<sup>3</sup> 22.5 in Australia,<sup>5</sup> and 21.6 in the United Kingdom.<sup>2</sup>

## INFECTIONS

Patients with CF are prone to respiratory infections and are routinely tested for the presence of numerous respiratory microorganisms. In their annual reporting, each national registry describes infection rates for common microorganisms. Across the United Kingdom, United States, Australia, and Canada, the most commonly reported infections are to *Staphylococcus aureus* and *P. aeruginosa*. For the latter, the prevalence of infections increases with age such that by adulthood over half of patients currently report it.<sup>1–3,5</sup> Data from the United Kingdom are presented in Figure 2.6, which shows a steep increase in the proportion of patients infected up to early adulthood after which it stabilizes.

Interestingly, infection rates for different microorganisms vary considerably between and within countries. For example, in 2011, 25.9% of patients in the United States had MRSA<sup>1</sup> compared with 2.6% in the United Kingdom,<sup>2</sup> 4.2% in Australia,<sup>5</sup> and 5% in Canada.<sup>3</sup> Conversely, *Burkholderia cepacia* was least common in the United States, 2.6% compared with 3.8% in the United Kingdom, 4.6% in Australia, and 5% in Canada. Within countries, there are differences between specialist CF units. In the United States, unit-level infection rates in children range between 10% and 59.1%.<sup>1</sup>

Keeping patients infection free for as long as possible is important as it has been shown that lung disease worsens more quickly after *P. aeruginosa* infection.<sup>83</sup> It has been observed that in children *CFTR* genotype functionality is an important predictor of age of first acquisition of *P. aeruginosa*.<sup>84</sup> Additionally, in analyses adjusted for *CFTR* functional class, ethnicity, and newborn screening, patients using pancreatic enzymes had an earlier age of initial acquisition. Other studies noted that being female, homozygous *F508del*, and prior *S. aureus* infections are also important predictors of early acquisition of *P. aeruginosa*.<sup>85</sup> The effect of prophylactic antibiotics on *P. aeruginosa* acquisition is debated.

## COMPLICATIONS

As well as the usual pulmonary and gastrointestinal complications traditionally associated with CF, patients with the disease can also experience other complications that are related to CF (such as cystic fibrosis–related diabetes [CFRD]). National CF registries collect data on a wide range of such complications. In the United Kingdom, the most common of

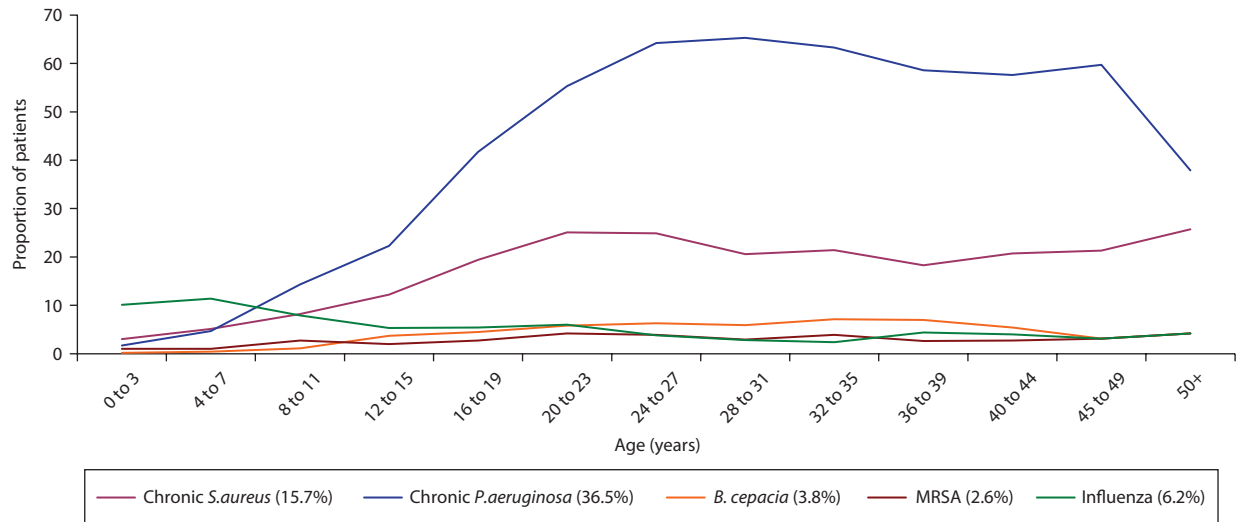


Figure 2.6 Age-specific prevalences of respiratory infections. (From CF Trust, *Cystic Fibrosis Trust Annual Data Report 2011, 2013.*)

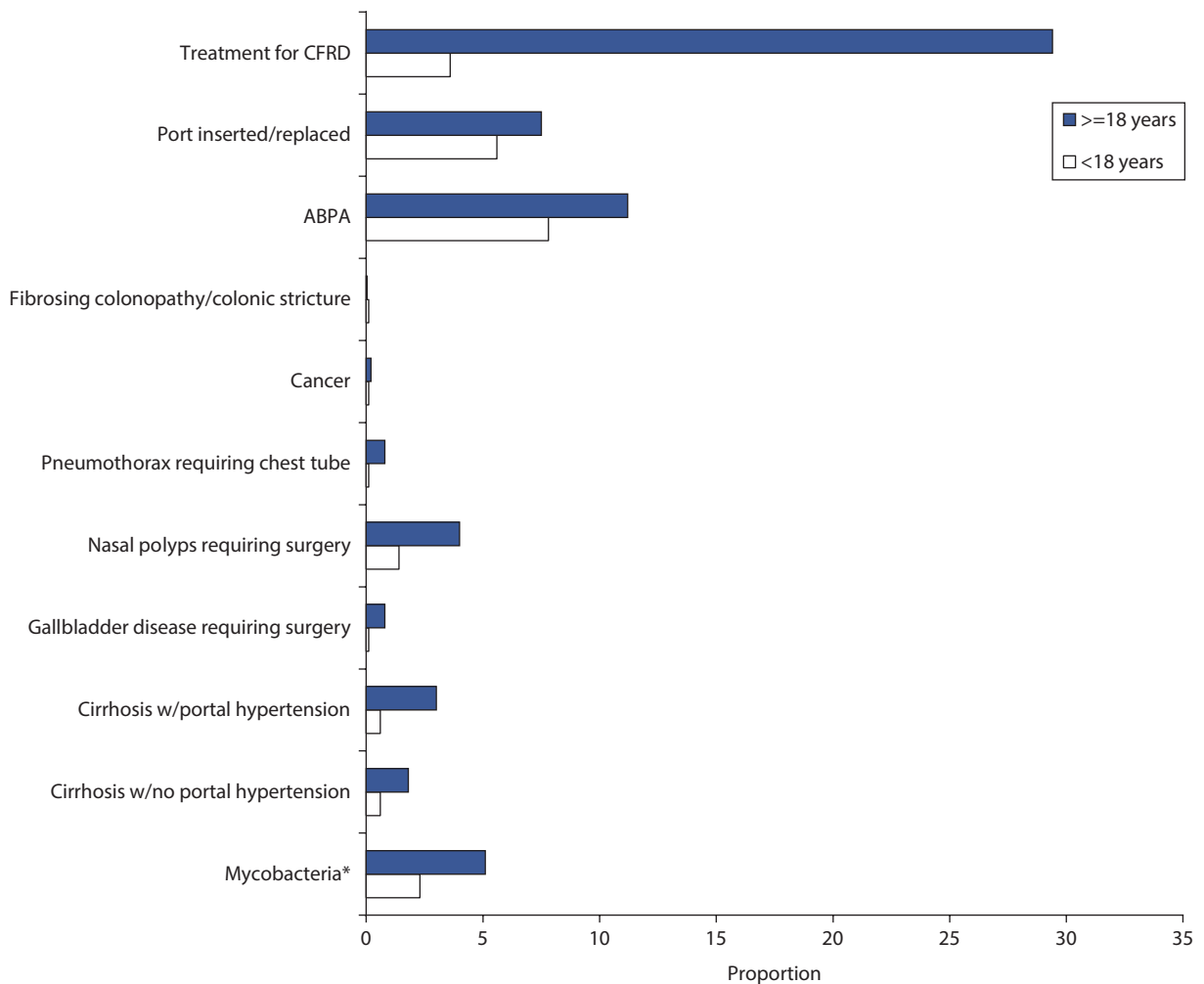


Figure 2.7 Proportion of patients with cystic fibrosis having different types of complications. The asterisk denotes nontuberculous or atypical. ABPA, allergic bronchopulmonary aspergillosis. (From CF Trust, *Cystic Fibrosis Trust Annual Data Report 2011, 2013.*)

these are CFRD and allergic bronchopulmonary aspergillosis<sup>2</sup> (Figure 2.7). In the United States, where a wider range of complications are reported by the CFF, the most common complications are sinus disease (29.2%), gastroesophageal reflux disease (28.9%), asthma (23.9%), and CFRD (18.9%).<sup>1</sup> When interpreting such data, it is worth considering the potential for ascertainment bias such that reported rates of complications may overestimate the true prevalence if patients with milder genotypes are not included, for example.

Many of the complications faced by CF patients become more common as patients grow older. As such, the improved survival of CF patients in recent years has meant that patients are facing health challenges uncommon in previous generations. Of the complications reported in the United Kingdom, only fibrosing colonopathy/colonic stricture was more common in children than adults. The US CFF reported that the proportion of patients reporting CFRD, bone disease, and depression increases with age<sup>1</sup> such that in patients 35 years and older at least a quarter of patients suffer from these conditions. A similar trend was documented in Canada for CFRD.<sup>3</sup>

## EDUCATION AND EMPLOYMENT

As patients with CF move into adulthood, there have been efforts to monitor not only their physical health but also other social parameters including education and employment. Treatment regimes in CF can be extremely time consuming, and hospitalizations for exacerbations take patients away from their normal routine. As such, there has been a concern that CF can have a detrimental effect on patient's educational attainment, job opportunities, and functioning at work.

### EDUCATION

The most extensive data available on educational attainment in CF patients can be obtained from national registry reports and a study conducted by Walters et al.,<sup>86</sup> who surveyed all UK adults with CF in 1990. In 2011, the US CFF reported that 92.4% of patients aged 18 years and older had at least obtained their high school diploma, with 33.8% obtaining a college diploma or completing a postgraduate degree.<sup>1</sup> In the United Kingdom in 1990, Walters et al.<sup>86</sup> showed that 85% of adults left school with some form of qualification, a result not dissimilar to the general population (in the 2001 Census survey, 81% of adults in England and Wales had some form of qualification; adapted from data from the Office for National Statistics licensed under the Open Government Licence v.1.0).

This positive experience was not universally observed, however. In a US study from the same era comparing adult patients with CF with healthy controls, CF patients were less likely to have a college degree than the healthy controls, although this difference did not reach statistical

significance.<sup>87</sup> A number of smaller surveys at single centers have shown that some patients felt that they had to leave their studies due to CF.<sup>88,89</sup> This is supported by Walter et al.'s<sup>86</sup> study, which showed that the 15% of adults who left school without qualifications had higher symptom scores compared to those who stayed on.

### EMPLOYMENT

Traditionally, with education—other factors remaining the same—come better employment opportunities. If CF patients are achieving academically, then it is worth exploring whether they are reaching their full potential in the workplace. In Walter et al.'s<sup>86</sup> large survey of adults with CF in the United Kingdom in 1990, 54% of adults were in paid employment. Twenty-one years later, 70.0% of patients aged 16 years and older in the United Kingdom reported being in work or study<sup>2</sup> and in the United States 58.4% of patients aged 18 years and older (the age by which most students will have completed high school) were in full- or part-time work or study.<sup>1</sup> In a recent large cross-sectional analysis of adult patients in Germany and Austria, researchers observed employment rates of 45.9% in 21- to 30-year-olds and 62.2% in 31- to 40-year-olds and 55.6% of patients over the age of 40 years had retired.<sup>90</sup> Other cross-sectional studies in the United States and elsewhere have noted varying levels of employment ranging from 48% to 72%.<sup>88,91–93</sup> Comparisons between countries and over long periods are obviously difficult, however, as local employment rates in the general population will differ. The results suggest, however, that most adults are in some form of employment or education.

Interestingly, patients in employment are not always in better health. In the United States, there was no evidence that FEV<sub>1</sub> differed by whether patients worked and both groups had low lung function.<sup>92</sup> It has been suggested that CF patients persist in working even with low lung function as it may serve as a distraction from their symptoms.<sup>92</sup> Other reasons for remaining in work despite low lung function include the opportunity to make a living and potentially benefit from health-care coverage through their employer. Conversely, in a small survey in Belgium, patients in work tended to have higher FEV<sub>1</sub> and were less likely to have *P. aeruginosa*.<sup>94</sup> Perhaps most convincing is a recent 15-year cohort study of adults using the United Kingdom's CF Registry database, which showed that those in employment tended to have higher BMI and FEV<sub>1</sub> and had spent less time in hospital.<sup>95</sup> As predictors of being in employment, however, the researchers showed that socioeconomic deprivation as measured at the postcode level modified the effect of FEV<sub>1</sub> such that FEV<sub>1</sub> had a smaller effect in the least deprived quintile and greatest effect in the most deprived.

When considering the type of work CF patients take on, it has been shown that they tend to take nonmanual jobs. Walters et al.<sup>86</sup> observed that adults with CF in work were more likely to be in nonmanual jobs compared to both the general population and their parents.<sup>86</sup> In a survey in the United States, 53.4% of adults in work were in professional,

technical, managerial, or professional roles.<sup>92</sup> In other US surveys, between 42% and 53% of adults were in professional or managerial roles.<sup>87,96</sup> In adult patients from a large center in France, 25% of those in work were in professional jobs and 39% were in intermediate jobs; 70% were in jobs described as “sedentary” or “light physical activity.”<sup>88</sup>

Small surveys in the United States and Australia observed that approximately half of adult patients reported that their career choice was influenced by having CF,<sup>91,96</sup> although only a quarter had discussed their career choice with their doctor.<sup>91</sup> In ideal circumstances, job duties can be altered to accommodate episodes of poor health. In the Australian survey 37% of patients said that they had had their job duties changed due to their CF,<sup>91</sup> although taking a different perspective in a French survey 55% felt that CF limited their job and 67% felt that CF prevented them from having a career.<sup>88</sup> At least a quarter of respondents in two of these surveys reported having taken a salary cut due to their CF.<sup>88,91</sup> It is unclear, however, whether this was negotiated and simply reflects shorter working hours.

## PROGNOSIS

Understanding the factors that influence survival is key to being able to implement successful interventions and much research has been done over recent years seeking to understand the factors. Early studies on smaller patient populations are now complemented by a wealth of studies taking advantage of large patient registries with long follow-up periods. When considering the research and comparing results stemming from these data sources, it is important to be aware of the many potential differences in patient cohorts, ascertainment of patients on various datasets, the patient mix, as well as varying clinical definitions and statistical methods. Broadly, however, the results from this work have identified a number of factors influencing prognosis, which can be broadly split into those that are modifiable and those that are unmodifiable.

## UNMODIFIABLE FACTORS

### CFTR genotype

Since the discovery of the *CFTR* gene and widespread genetic testing of CF patients, it has become possible to assess the impact of genotype on survival. Studies have generally focused on whether or not the patient is homozygous *F508del* or examining the functional class of the genotype, classes I–III being classed as more “severe” and IV and V being “milder.” Compared to homozygous *F508del*, those with other genotypes were not found to have different survival.<sup>97,98</sup> When incorporating data on functional class, however, researchers have found that those with a more severe genotype had worse survival. Lai et al.<sup>99</sup> found that after adjusting for characteristics at presentation, patients

with a more severe genotype (other than *F508del*) had worse survival than those who were homozygous *F508del*. Those with a milder genotype had better survival. McKone et al.<sup>57</sup> found that the negative effect of a more severe genotype was independent of pulmonary function and compared to patients who are homozygous *F508del* those with *G551D*, *DI507*, *R117H*, *3849+10kbC>T*, and *2789+5G>A* mutations had improved mortality rates.<sup>56</sup>

### Pancreatic sufficiency

Pancreatic sufficiency is often correlated with less severe *CFTR* genotypes<sup>59</sup> and has been found to be associated with mortality<sup>100</sup> but not necessarily after adjusting for genotype and other nonmodifiable characteristics.<sup>57</sup>

### Sex

A considerable amount of research has sought to assess whether there are meaningful differences in survival between men and women, and the results of research to date have been varied. Early studies using national or registry data found that females were less likely to survive beyond the median age.<sup>64,101,102</sup> A number of studies using regression models that adjusted for clinical and genetic characteristics have also found that despite this adjustment survival is poorer in females.<sup>64,97,99,100,103–105</sup> In an analysis stratified by age, researchers found that the differences in survival between males and females only reached statistical significance in childhood and in the teenage years.<sup>106</sup> Sex also features in a number of multivariate prognostic models,<sup>107–109</sup> although not all.<sup>110–112</sup>

More recently in Italy, however, researchers found in a follow-up study of children that survival was no different between males and females, although females had a higher excess mortality due to CF compared to males.<sup>113</sup> Assael<sup>68</sup> also found no evidence of a gender difference in a much smaller study in Verona as in other smaller studies elsewhere.<sup>98,114</sup>

Adjustment for potential confounders is important to attempt to understand whether the drivers for any observed gender differences are due to being female or poorer clinical characteristics in these patients such as FEV<sub>1</sub> and BMI. Furthermore, it is also worth making the distinction between “sex” as a biological variable (hence its inclusion in this section of nonmodifiable factors) and “gender,” which incorporates the associated attitudes and behaviors.<sup>115</sup> The influence of sex on incidence and outcomes of CFRD is discussed in Chapter 19.

### Socioeconomic status

A number of studies have found an association between markers of socioeconomic status and health outcomes both within and outside the CF patient population and in countries with and without universal health-care systems. In the United Kingdom where all patients have access to the National Health Service, Britton<sup>101</sup> observed that patients

with CF from nonmanual occupational backgrounds were more likely to survive beyond the median age than those in manual jobs. This difference was observed again 20 years later in the United Kingdom by Barr et al.<sup>64</sup>

In the United States, Schechter et al.<sup>116</sup> observed that patients receiving Medicaid support were at a higher risk of death and that the relationship was independent of sex, age, race, and pancreatic sufficiency. When FEV<sub>1</sub> was added to the model, however, the association was no longer significant, suggesting that such differences may be driven in part by poorer baseline clinical characteristics. Also in the United States, but using a different measure of socioeconomic status, O'Connor observed that the incidence of death decreased with increasing household income after adjustment for age at diagnosis, characteristics at diagnosis, and sex.<sup>117</sup>

The impact of socioeconomic status on other clinical outcomes is described later in this chapter and in Chapter 9.

## Characteristics at diagnosis

It may be reasonable to assume in a genetic disease that patients' clinical characteristics at baseline—prior to receiving specialist care—might influence survival. Findings in this area, however, are mixed and depend in part on the groups being compared. In the United States, it was observed that patients who were identified due to the presence of meconium ileus—and, separately, those presenting with symptoms—had shorter survival than those who were identified by neonatal screening even after adjusting for a cohort effect.<sup>99</sup> Patients presenting at an older age and those presenting with nonclassical respiratory or gastrointestinal symptoms were also less likely to have reduced survival. These results suggest the presence of a milder phenotype with improved survival.

Conversely, however, in Verona where neonatal screening had been in place for 30 years, researchers found no difference in survival according to whether patients were diagnosed by screening, symptoms, or the presence of meconium ileus<sup>68</sup> and in Israel Efrati et al. found that survival did not differ by whether or not the patient had meconium ileus.<sup>118</sup>

## MODIFIABLE FACTORS

### Pulmonary function

In follow-up studies where clinical data are available, FEV<sub>1</sub> % predicted at “baseline” (whenever this might be) has routinely been found to be positively associated with survival.<sup>57,98,100,104,105,119</sup> Kerem found that both FVC (forced vital capacity) and FEV<sub>1</sub> predicted survival.<sup>103</sup>

A few studies have examined whether clinical measurements taken during exercise testing are predictive of subsequent survival. Results from these have been mixed where some found that VO<sub>2</sub> was predictive of survival rather than FEV<sub>1</sub><sup>120</sup>; yet another found that in a model containing both variables only FEV<sub>1</sub> was predictive.<sup>121</sup>

## Nutrition

The importance of maintaining good nutritional health in CF patients has long been appreciated.<sup>122</sup> Nutritional health can be measured in a myriad of ways, whether using height, weight, or BMI using raw values, percentiles, or z-scores. Regardless of the measure, most studies have found that patients in bad nutritional health had a poorer prognosis.<sup>57,98,100,103–105,123,124</sup> Perhaps most famously, a study comparing survival at a CF clinic in Toronto with one in Boston showed improved nutritional outcomes and survival despite similar lung function in Toronto where patients were on a high fat diet compared to Boston where patients had a low fat diet.<sup>122</sup> The researchers suggested that the improved survival in Toronto may be due in part to the improved nutrition of patients there.

## Respiratory infections

The role of respiratory infections on prognosis has been studied extensively, and most studies have focused on the roles of *P. aeruginosa* and on *B. cepacia*. Disentangling their effect—independently of pulmonary function—has not been straightforward, however.

For example, mucoid *P. aeruginosa* infection was found to be associated with worse survival, but the effect was no longer statistically significant when FEV<sub>1</sub> was incorporated into the model.<sup>119</sup> Similarly, in a large national registry study in Canada researchers found that after adjusting for sex, FEV<sub>1</sub>, and *B. cepacia* infection, infection with *P. aeruginosa* was no longer significantly associated with survival.<sup>104</sup> Conversely, large registry database studies in the United States found that the risk of death was higher in patients with *P. aeruginosa* even after adjusting for FEV<sub>1</sub> and other characteristics.<sup>57,100</sup>

Patients with *B. cepacia* had worse survival than those without,<sup>125</sup> and patients are less likely to reach the age of 18 years.<sup>99</sup> Worse survival has been observed after adjusting for sex, FEV<sub>1</sub>, and *P. aeruginosa*.<sup>104,105</sup> Chamnan<sup>105</sup> found similar results recently in the United Kingdom, although here they adjusted for *S. aureus* rather than *P. aeruginosa*. The relative importance of *B. cepacia* over *P. aeruginosa* was also found in a single-center study where patients infected with the former were matched with those infected with the latter. Survival was shorter in those infected with *B. cepacia*.<sup>126</sup>

More recent work in the United States suggests that MRSA infection can also predict worse survival after adjusting for other infections and patient characteristics.<sup>109</sup>

## Cystic fibrosis–related diabetes

There is increasing interest in the potential effects of CFRD on survival. A recent study in the United Kingdom showed that survival was worse in 10- to 29-year-olds with CFRD compared to those without and that it is an independent predictor of survival after adjusting for other covariates.<sup>105</sup>

A smaller, earlier study in the United States suggested that the effect of CFRD on survival might be most evident in females<sup>127</sup> (see Chapter 19).

## PREDICTIVE MODELS

A number of predictive models have been developed to provide clinicians with estimates of survival probabilities in patients with specific clinical characteristics. These have differed in timeline and composition. Using data from a single UK center between 1969 and 1987, researchers in the United Kingdom developed a model for predicting 1-year survival using hepatomegaly, height, FVC, FEV<sub>1</sub>, and white blood cell count.<sup>111</sup> In the United States, Liou et al. developed a 5-year survivorship model using registry data, which included age, FEV<sub>1</sub>, gender, weight for age, whether or not the patient was pancreatic sufficient, CFRD, *S. aureus* infection, *B. cepacia*, and the number of exacerbations.<sup>107</sup> Another model using US Registry data predicting 2-year mortality included age, height, FEV<sub>1</sub>, hospitalizations, the number of home IVs, and respiratory infections (*B. cepacia* and *P. aeruginosa*).<sup>112</sup>

There is also some evidence that models developed in one setting may not be suitable in other patient populations. Liou et al.'s model, for example, required some refinement in the Italian context and was reduced to including FEV<sub>1</sub>, *S. aureus* infection, *B. cepacia* infection, and the number of pulmonary exacerbations per year.<sup>110</sup> It is unclear, however, whether this refinement is a characteristic of the different patient populations, different health systems, period of study, or sample size.

## MODELS OF CARE

It has long been recommended that patients with CF receive their care from specialist providers, a trend also seen in other disease areas justified, at least in part, on the premise that centers treating more patients will deliver better outcomes.<sup>128</sup> Demonstrating conclusively through observational studies that such models of care are responsible for improved outcomes, however, is difficult due to the very nature of their study design. Furthermore, extrapolating from the experience of one health-care system to another is problematic and what constitutes a specialist center may vary over time and between countries as will the nonspecialist alternative.

Nonetheless, a number of studies have attempted to assess whether specialist care delivers better outcomes than nonspecialist care. One of the earlier studies compared mortality rates in England and Wales prior to the widespread establishment of specialist care with mortality rates in Queensland, Australia, where all patients were seen at a single specialist clinic.<sup>129</sup> Here the researchers observed significantly higher mortality rates in England and Wales, which they attributed to the lack of specialist care. In Denmark

researchers also noted that patients receiving centralized care had improved survival,<sup>15</sup> and a small study in Holland also noted an improvement in those receiving specialist care.<sup>130</sup>

Other studies took advantage of the fact that patients' lifetime contact with specialist care will vary as some will only gain access to specialist care later in life. In Australia, researchers noted that patients who had continuous specialist center care from birth had improved height and weight measures in their early teens, but they noted no improvement in FEV<sub>1</sub>.<sup>131</sup> Mahadeva et al.<sup>132</sup> made a similar observation in adults in the United Kingdom when they compared those who had only just begun treatment in a specialist clinic with those who had started earlier and those who had always received specialist care. They observed an increase in BMI with increasing duration of contact with specialist services, although no significant improvement in FEV<sub>1</sub> occurred. Conversely, in Belgium researchers noted that patients who were referred earlier for specialist care had higher FEV<sub>1</sub> and less *P. aeruginosa*.<sup>133</sup>

In the United Kingdom, Walters et al. undertook a number of large cross-sectional surveys of adults with CF assessing their access to specialist care. In 1994, it was noted that approximately two-thirds of adults received specialist care and that those attending these centers had lower symptom scores than those receiving nonspecialist care.<sup>134</sup> By 2000, access to specialist care had increased and meaningful differences in the type of care delivered were noted where patients attending specialist centers were more likely to have access to allied health professionals and had more access to routine investigations such as sputum samples, blood tests, and lung function testing.<sup>135</sup> The importance of access to such routine investigations was highlighted in a US study, which used national registry data to compare the top 25% of US centers with the bottom 25% (based on center-level FEV<sub>1</sub>) and observed that the best-performing centers monitored patients' clinical status more frequently and made more lung function measurements and more frequently tested for respiratory infections.<sup>136</sup>

Recognizing the need for both specialist and local care—particularly in more isolated regions—"shared care" systems have been developed. In this model of care, patients receive care locally as well as from clinicians at specialist centers. The frequency of specialist contact and nature of such contact will vary between centers and local clinics. Conveniently, this model of care also provides an opportunity to determine whether there is a dose-response association between amount of specialist contact and health outcomes. This was recently studied in Wales, where a complex shared care arrangement exists between the main pediatric center in Cardiff and its network clinics where patients have local care with three visits per year in Cardiff (referred to as "hybrid care") and local care with an annual review in Cardiff (referred to as "local care").<sup>137</sup> The researchers did not observe any differences in nutritional outcomes or therapies used between the three models of care, but FEV<sub>1</sub> was found to vary and was lowest in those receiving local care and highest in those receiving full center care. The results suggest that the amount of specialist

contact is important. Conversely, in an Australian study of children receiving full center care and varying degrees of “outreach” care, researchers noted no observed differences in FEV<sub>1</sub>, *P. aeruginosa*, or height/weight z-scores.<sup>138</sup> Similarly, in the Netherlands researchers noted no differences in annual changes in FEV<sub>1</sub>, FVC, and BMI between pediatric patients receiving center, local, or shared care.<sup>139</sup>

The lack of consistency in results between studies may be due to a host of factors from the limitations noted earlier to issues of sample size when specific local networks are compared as these tend to be smaller.<sup>138</sup>

## SOCIOECONOMIC STATUS

As noted previously, a number of studies have observed that individuals from more socioeconomically deprived backgrounds have poorer survival<sup>64,97,101,116</sup> and this occurs both in fee-paying health-care systems and those with universal health care. Analyses examining other clinical end points have also observed differences in FEV<sub>1</sub><sup>116,140–143</sup> and nutritional outcomes.<sup>116,140,142,143</sup> Quittner et al.<sup>140</sup> also noted that Medicaid patients reported poorer quality of life in analyses.

Interestingly, while FEV<sub>1</sub> was found to vary by neighborhood-level income in Canada<sup>141</sup>—a result also noted in the general population<sup>144</sup>—no association was observed between income and hospitalization for respiratory conditions after adjusting for FEV<sub>1</sub>. The researchers postulated that this lack of association may reflect that most admissions were respiratory related. In the United States, however, Schechter et al.<sup>116</sup> noted that among children those on Medicaid were more likely to have hospitalizations and pulmonary exacerbations despite adjusting for FEV<sub>1</sub> and other factors.

Recognizing differences in outcomes by socioeconomic status, a number of large studies of children in the United States have sought to identify whether the treatments prescribed to patients differed by socioeconomic status. No consistent associations were observed between a variety of measures of socioeconomic status and the prescribing of chronic therapies.<sup>143</sup> When antibiotic use was studied, no associations were observed, although when considering IV antibiotic prescribing in children under the age of 6 years there were higher treatment rates in those with lower socioeconomic status.<sup>145</sup>

It is recommended that patients with CF receive care in specialist centers and evidence from the 1980s and 1990s suggested that even in the United Kingdom, where health care is free at the point of use, patients from more socioeconomically deprived backgrounds were less likely to receive such care. In the late 1980s, Penketh et al.<sup>89</sup> noted that patients from manual occupational backgrounds were underrepresented at a large specialist adult clinic. Walters et al. noted that adults from manual occupation backgrounds were less likely to be seen in a specialist adult clinic, although when grouping pediatric and adult clinics this association disappeared.<sup>134</sup>

Studies in the United States have shown somewhat mixed findings when considering the amount of contact with specialist services. Schechter et al.<sup>116</sup> did not observe a difference in the number of clinic visits by Medicaid status, whereas Nathanson et al.<sup>146</sup> noted that patients in managed care (whether Medicaid or other) were less likely to be seen in their specialist clinic every 4 months as recommended.<sup>147</sup> The reasons for this lack of consistency could be due to subtle yet meaningful differences in measures of socioeconomic status.

Beyond the use of therapies, Quon et al.<sup>147</sup> observed that those on Medicaid who were being considered for a lung transplant in the United States were less likely to be accepted onto the transplant list even after adjusting for disease severity and transplant contraindications.

## QUALITY IMPROVEMENT

The notion of quality improvement is well-established in the manufacturing sector. Systems are studied to identify “failures”; then investigations are made to identify the processes responsible for these failures so that improvements can be made. Many in health care have sought to adapt the methods used to study systems in factories to those in hospitals with the aim of improving the care delivered to patients. Recognizing the many stakeholders in health care and the role each plays in delivering good outcomes, it has been suggested that quality improvement in this area is “the combined and unceasing efforts of everyone—healthcare professionals, patients and their families, researchers, payers, planners and educators—to make the changes that will lead to better patient outcomes (health), better system performance (care) and better professional development.”<sup>148</sup> The principles of quality improvement and use of registries to improve care are discussed in Chapter 26.

Although it has been noted that there are difficulties in getting quality improvement studies published in peer-reviewed journals,<sup>149</sup> a number of studies have been published in the last 5 years. Adopting a quality improvement approach has yielded improvements in BMI<sup>150</sup> and FEV<sub>1</sub><sup>150,151</sup> in pediatric clinics, identified potential failures in newborn screening before they occurred,<sup>152</sup> helped to develop a standardized strategy for evaluating the nutritional status of patients,<sup>153</sup> improved clinician adherence to prescription guidelines at a pediatric center,<sup>154</sup> and improved the success rate for sweat testing in infants.<sup>155</sup>

To monitor systems, data must be collected and large national patient registries, such as those in the United Kingdom, United States, Canada, Australia, Denmark, and Germany, are rich data sources for such monitoring. The CFF has long supported quality improvement initiatives, and since 2006 they publicly report center-specific outcomes with an aim to “accelerate the rate of improvement in CF through benchmarking.”<sup>156</sup> A benchmarking

approach has also been recently launched in Germany using patient registry data.<sup>157</sup>

These initiatives at local and national levels illustrate the desire within the CF community to learn and improve the care they deliver.

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## Living with cystic fibrosis: The voices of patients and families

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MATT BENN, HELEN BENN, JESS HARRISON, KEVIN PASSEY, EMILY HOYLE, RUPERT PEARCE GOULD, AND FRANCES PEARCE GOULD

### SCREENED CYSTIC FIBROSIS BABY'S PARENTS

MATT BENN AND HELEN BENN

Thinking about it now (2 years on), the initial shock at the diagnosis was all the greater for having followed so soon after the happiest and most wonderful day of our lives. Being first-time parents, 3 weeks (the age at which Matilda was diagnosed) into our new roles, we were still very much finding our feet. Discovering that Matilda had this thing called “cystic fibrosis” at the same time meant nothing and everything to us, as we knew so little about the condition, but we were somehow fully aware that this would affect her for her whole life.

Helen received a phone call early on Monday morning to say that a specialist would be coming round to our house to discuss the results of Matilda’s heel-prick test. The visit didn’t happen until later that day, allowing for as much deliberation and pacing of the hallway as the tiny Matilda would allow us. The specialist (a nurse from our regional CF center) showed admirable compassion and sensitivity when discussing such awful news with two people whose worlds had been blown apart following the revelation. She advised us that an appointment had been made at the CF center for the following day, at which we could meet the clinicians who would be involved in Matilda’s care. Although the speed of the organization was impressive, this still left an evening for the inevitable but ill-advised Internet homework to take place.

The next day’s appointment served as an introduction to the regime that would commence in the following days (and which will last for the whole of Matilda’s life) and helped set us straight regarding the various pieces of amateur research

we had managed in the meantime. (In fact, some of the consultant’s most worthwhile advice suggested that we disconnect our Internet for a few days.) It became apparent at this meeting that the clinical staff who would be caring for Matilda already took a great interest in her as a person (and not just as patient X), and the consultant’s language and personable nature made us feel more positive even at this very early stage. We also felt reassured (rationally or not) that some of Matilda’s behavior (for example, her appetite) was somehow “explainable” by the biology of a CF sufferer. We were then invited to return a couple of days later for a more comprehensive introduction to the condition and the practical ways in which our lives would change as the parents of a CF child.

In the meantime, we faced the issue of how, and how much, we should tell our friends and family. Should we tell anyone at all? Would people think differently of us, or of Matilda, if they knew what we knew? Would they think it was our fault? Was it our fault? We were repeatedly assured that it wasn’t, but we felt a sense of guilt nevertheless. Ultimately, it was our decision to have a child, so who else’s fault could it possibly be? We settled on telling immediate family and a few close friends, however hard it was to do so; in hindsight, this proved sound judgment, given the support and encouragement we received at that time. This also taught us that we would probably never really come to terms with the news ourselves—it would of course get easier and 2 years down the line it unquestionably is, but CF reminds us every day that it’s here and here to stay.

The 2-day “induction” session at our regional CF center marked the start of the rest of Matilda’s life. From now on, the medicines, dietary considerations, and physiotherapy would warrant daily attention. We were allowed to bring immediate family to both days (not least since both sets of Matilda’s grandparents had expressed great interest in

not only learning about her CF but also helping to treat it where possible), which, from many angles, was an invaluable element of the induction. Apart from the moral support, the extra pairs of ears to take in the enormous amount of information proved priceless. It was then that the excellence of the clinical team became truly apparent—not only did it manifest itself in their positivity and compassion but the way the different disciplines integrated and communicated with each other encouraged us that Matilda was being looked after by a truly professional group. We were treated like adults (when, in reality, we were as clueless as any children are on their first day at school) and offered involvement in decision making and explanations of the science behind (for example) some of the medication we would be administering. Most of all, we never felt that we were on our own, and for this we will always be grateful.

We've learned that CF presents a new set of challenges in every stage in a child's development, as with any aspect of parenting. Different features of Matilda's regime vary, both positively and negatively (for example, her ability to cope with the evolving physiotherapy routine or the knock-on effects of changing her balance of medicines), so there is no time to take our eye off the ball. Mercifully, we have always felt supported when contacting the health professionals; no symptoms are not worth discussing and we are never made to feel like a nuisance, despite our intuition! We are also thankful that we live in an age where communication with fellow CF families is easier than it's ever been, particularly among a set of individuals who are advised never to meet face to face. The Internet brings many of us who need each other closer together, and we have discovered that the CF community is a resilient and spirited one.

At the back of our minds is always that one day Matilda will have to take on board all that we have learned and more. Part of us enjoys the innocence demonstrated by a child who knows no better, who now swallows medicine like it's orange juice and who hops up on the sofa for physiotherapy as regularly as she brushes her hair, but we know that one day she will learn that not everyone does this and that actually she isn't as well as most other people. We know that our most important job is to be as positive for her as possible, so that when this day comes she is positive too.

## TEENAGER

### JESS HARRISON

At my current age of 15, I have learnt how to cope with my condition. I have learnt not to let it get in the way. I have also learnt to live life to the full and enjoy every moment. It hasn't always been like that though. I was diagnosed with CF at the age of 18 months. This was after 18 months of solid fighting and arguing from my parents who insisted that something was not right. At 10 months, I developed

meningitis; I was hospitalized for 1 week, and my symptoms of diarrhea continued. Both my mum and dad realized that I had something else. After battles with doctors for the next 8 months, someone listened. I was diagnosed with CF at merely 18 months.

From then on, I have had to take tablets before each meal and each fatty snack. I also do a nebulizer, which consists of Promixin and saline. This is inserted into an i-neb. I do this twice a day on top of doing a flutter. On average, each time takes 10 minutes; this is very useful as it only takes a short time and means that my day is not disrupted. I love hanging out with friends and often sleeping round their house. As my nebulizer is only small, I bring it with me; I also bring all my morning tablets as well as my usual tablets. As I have gotten older, I have gained more confidence to talk to my friends and anyone I meet about my condition. This means I am not ashamed about taking my tablets in front of them. When I was younger (primary school), I was taken into the receptionist's office to take my tablets away from the other kids. When I joined secondary school, I made the decision to take them in front of everyone. This way, I feel responsible and in control.

Throughout secondary school, I have not let my CF get in the way of anything I do. I take part in all lessons including games and physical education, as well as making sure I lead an active life both in and out of school. This was demonstrated recently when I took part in the school's cross-country race and managed to come 16th out of 120. A triumph for me; it didn't come easy though as one teacher insisted that due to my condition I sat out and helped instead of competing. However, this annoyed me so I got even more competitive and pushed myself until I crossed the line and got a heartfelt well done from my teacher. Due to my condition, I have been "discriminated" from doing some events as people are afraid of the seriousness of it. I have been told I could not scuba dive at a Guide camp, as well as being told I cannot run. However, these just make me want to do more and make me want to prove myself.

Outside school, I take part in a range of activities including Duke of Edinburgh award, Guides, helping out at Brownies, drama, singing, and tennis. Each activity requires a physical element and the confidence to talk to whomever if they ask about my tablets. When I explain my condition, many people respond with "oh you poor girl" and so on. My reply? Why? I cope with it, I lead a happy and healthy life, and I live a basically normal life. As I have gotten older, I have also realized that some people try to joke about the condition to make it seem less serious. This is shown as the joke I always get when I explain how many tablets I take, "whoa, you take so many tablets do you not rattle?" Every time. It used to annoy me, but now I have just learned to laugh along as people cope in different ways.

Having CF does mean I have had to grow up faster. This is because I have more responsibility than most others my age have. I have to wake up and first think about nebulizer, tablets, and so on, whereas others first think of makeup, shower, and so on.

I wish I could meet and talk to others my age who also suffer from CF. This is because they would be going through the same thing as me and we could share experiences. Having CF means that when I am at the Brompton Hospital I am separated from other kids and I am put in a room on my own; I can't meet or talk to any of them. I used to get annoyed by this as I thought it would be great to talk to others, but as I have gotten older my parents have told me everything about the condition and have told me that meeting other children with CF could be a risk to me and them.

I understand that CF will shorten my life, but that's okay! I have known this from a young age, and I feel this has helped me to grow up even more. I may be 15, but I know what I want to do when I'm older and how if I want a family I need to do it sooner rather than later due to my condition. A couple of years ago, I asked what the risks were of my children getting CF. The doctor gave me a thorough explanation, which has given me a much larger knowledge on passing down CF throughout generations.

I try not to let CF affect me every day, and to me it doesn't. But the things I do (nebulizer, tablets, and eating more salt) have just become a routine for me. I make sure I live life to the fullest and take every opportunity as I know that my life will be shorter, but doing this enables me to have a good but perhaps shorter life. My friends and family are a big support and treat me just like everybody else, and to me I am just like any other 15-year-old girl.

## WELL CYSTIC FIBROSIS ADULT

KEVIN PASSEY

### INTRODUCTION

I am 53 years old and have CF. I have been happily married for 27 years. I run my own computer software company, and I live in a beautiful part of West Sussex. I was diagnosed with CF at the age of 9 months. I have been a patient at the Royal Brompton Hospital in London for many years and work as their CF advocate.

I have a very busy and hardworking business life, with clients all over the world; I am extremely lucky to have a great social life, going on many holidays including skiing and golfing.

CF is a very important part of my day-to-day living; however, I do not let it get me down or rule my life. I do hope that by writing this I will give other CF sufferers, their parents, and loved ones determination; hope; and above all a sense of normality, which is so important to me.

### DIAGNOSIS

I was diagnosed with CF when I was 9 months old. At this time, not very much was known about the disease and

specialist centers did not even exist; I just went to the local hospital chest clinic.

When I was a newborn, my mother tells me that she would constantly take me to the doctors because she knew I was unwell, suffering from chest infections, and my nappies would be full of, what she describes as, "melted butter." However, nobody would believe her; she was told she was suffering from postnatal depression, and even my father thought this might be true and she was told to have a holiday and everything would be fine. The holiday was cut short as I became very unwell, and this time she wasn't going to take no for an answer. She took me back to our GP; he took one look at me and an ambulance was called. Finally, they were taking her seriously.

After many tests I was diagnosed with CF, and both my mother and father were told that they were lucky I had lived to 9 months without any treatment and that I would never get any better and would never become a teenager. The best they could hope for was that I would live to between 5- and 8-years-old.

### EARLY YEARS

Once on medication for my condition, the early years were pretty uneventful from what I can remember. I went to school as normal, and I didn't really miss out on any activities. I probably got more colds than my friends, and I do remember going into hospital for a nasal polypectomy. I used to go for checkups with my parents, but I wasn't on any long-term antibiotics. I just had to take Pancrex powder with my food. I didn't really understand much about CF and just got on with my schooling. It was when I got into my teenage years that I started to understand a little more.

### TEENAGE YEARS

At 15, the polyps had returned and were affecting my breathing so I had another nasal polypectomy. This encouraged me to ask questions about my CF, so my parents started getting information from the CF trust. I went to one of their meetings with my parents, and it was explained that CF sufferers would not live much past 15. I can remember looking at my parents and thinking to myself, that is not great, what is the point of taking any drugs. I was still taking Pancrex for my digestion at the time. I might as well just have a good time and make the most of what little time I had. So that is what I did. During this time I met my girlfriend, and then things really changed. I had found someone that I really liked, and she started to help me take my CF a lot more seriously. At that time, I used to go for checkups every 6 months; but there was no real CF expertise and I can remember on one visit being told that there really was not much they could do for me, that I was fairly well, and to just get on with life. It was at the same visit that they told me, "and by the way you will never father children." I was devastated; I had just found a girlfriend, and she was not going to stay with me after that news. But of course that

wasn't the case; we married some 10 years later and have been happily married for the last 27 years.

## MARRIED LIFE

I married Jane in May 1985 after a 10-year courtship, I was 25, we had a fabulous wedding, and we honeymooned in Cornwall. Shortly after getting married, I had my final polypectomy.

My early working life saw me traveling all over the world writing software; I loved it, but I felt that I needed new challenges. I had many contacts in the industry so I decided to set up my own company. Jane agreed she would leave the BBC and help me, so KDP Software, Ltd., was established. Our first contract was working for a large stationery company based in Enfield.

We gradually employed more computer programmers and rented some offices in Hatton Garden in the center of London. Business was great, but my health was gradually deteriorating. Commuting from Ruislip to London every day had a huge impact because I picked up infections on the underground, so we decided to sell our first house and buy an apartment in Earls Court so that I could drive to work. However, things still did not improve. I was still not being treated for my CF, I would cough most of the day and night, and my weight dropped to below nine stone. After a trip to my local GP, the turning point came. I was referred to the adult CF unit at the Royal Brompton Hospital, and I finally started to receive the treatment that I so badly needed.

However, this brought new challenges for me; how did I fit the whole new drugs regime into my busy working schedules. I was traveling all over the country at this time and employing 10 programmers, all working on different projects. It was not going to be easy.

But this was the best thing that could have ever happened to me. I started to take Creon; I was given daily oral antibiotics and numerous vitamins. I really started to take my health seriously; this was now more important than anything else. Jane used to help me morning and night with physio, and things changed dramatically. I barely coughed at all, and my weight increased to 12 stone. I had more energy, and life returned to some normality.

In hindsight, I think I had just got used to feeling so unwell and thought this was a normal; after all, I did suffer from CF and I think this is one big issue with CF sufferers that really needs to be addressed.

My physio regime became much easier with the introduction of the flutter, which I make sure I do at least once a day. Now I don't need to call upon my wife so much to complete that part of my health care.

However, further new challenges were to come. On a routine visit to the hospital, I asked my consultant about becoming a father. Jane and I both love children and wondered what the chances were of me fathering my own. I had been told there was no chance that men with CF could father children, but I thought there was no harm in asking.

We were referred to Prof. Winston's clinic at Hammersmith Hospital, and I became the first CF male to undergo epididymal aspiration. We underwent five IVF procedures using the ICSI technique, we achieved 16 embryos, all girls. We were over the moon and so were the consultants; maybe CF men could father children after all. However, it was not meant to be. We lost them all, and I think this was probably a very low point in both of our lives.

However, we decided we could not let this get us down. We only wanted our own children. We couldn't have them, so we put our heart and soul into our business.

As life progressed and I got older, it was felt that maybe my regimen should change with the introduction of nebulized antibiotics. I have been lucky enough not to need IV antibiotics on a regular basis; in fact, I have only ever needed them once.

I think at the time, when it was suggested that I do nebulized antibiotics, I felt my health was on a downward spiral, what next. I gradually got used to the idea, and it is very much a part of my daily life; so I started to nebulize rhDNase once, in the morning, and Promixin twice, once in the morning and last thing at night. Then much more recently, I started Tobi on alternate months. This seems to be working very well, as I rarely get chest infections.

Diet is an extremely important part of keeping well with CF; but fortunately this has never been an issue for me since I got married, as my wife insists I eat a very healthy diet and luckily for me she is an extremely good cook. Of course, eating the odd curry or kebab can't go amiss and I probably drink a little too much beer, but nobody is perfect!

Living with CF and being married of course had its challenges, but then life is one big challenge with or without CF. I think keeping positive, doing plenty of exercise, and keeping active is very important and key to staying well. I ride a mountain bike, and it certainly makes a difference to my breathing.

## LIFE AT 53

On November 25, 2012, I will be 53, and life is pretty good. I have a successful business, a lovely home, and a very happy marriage. We try and get a skiing holiday each year and I play golf as much as I can. We also have a West Highland white terrier who requires a lot of walking, which of course keeps us both very active.

So how did I get here with CF? If I am honest, I have never let it get me down. I have always been optimistic, and I am lucky that all my family and friends have never treated me any differently to the rest of our family and friends.

I don't dwell on the illness even if it does take me quite a while to get out in the morning, because of the time it takes to do physio and nebulizing, but this is key to a long and healthy life. Also helpful is taking all the advice the consultants at Brompton give and making sure I give them the correct feedback, not just telling them what I think they want to hear, going for regular checkups and trying to exercise as

much as possible. Most importantly, I try to maintain 100% compliance with my drug and vitamin regime; this is not always possible, but it is something that I think has made a big impact on my quality of life. My physio in the morning is something I feel is very important, much like going out in the morning without brushing your teeth, you just wouldn't miss it.

In summary, I get on with my life and I am looking forward to the future with a very positive attitude.

## CYSTIC FIBROSIS PATIENT WITH SEVERE CLINICAL COURSE

EMILY HOYLE

On the outside, people with CF look completely normal most of the time. However, on the inside it is a completely different story. In some ways, this is a blessing and in some a curse. It means we can live almost normal lives in some respects. But on the other hand, we do not always get the "attention" we require, for example, a seat on a train or bus; no one will move for you as you look "fine." On the flip side, we can walk into a room and be treated like everyone else and momentarily forget everything we are dealing with. CF is a personal and sometimes embarrassing topic.

## MY STORY

As a child, growing up with CF was relatively simple. I did my daily nebulizers, physiotherapy, and cocktail of medication, but I was well protected from the harsh reality of what it meant to have CF and so blissfully grew up just thinking that my life was like everyone else's plus a few drugs. However, when I was 11 I discovered the life expectancy for CF sufferers. My brother, who also has CF, was told he was infertile. I decided on hearing this news that I didn't want any shocks myself so asked the doctor what surprises he had in store for me. I was not prepared for the answer. The average life expectancy for someone with CF when I was told was thirties. So, at the tender age of 11 I grew up. I realized that if I was to die in my thirties there would be a long decline for many years beforehand, which was a lot to stomach.

I didn't discuss it with my friends (as I didn't think that they would be able to empathize with me); I did not want to upset my parents with my fears, as I also realized that I was likely to die before them and I could only imagine the devastation for them. So I decided then that life just went on and I had to do everything possible to maximize my chances.

While at university, my health deteriorated. I would frequently get stopped in the street and be told to stop smoking, having never smoked a cigarette in my life. Over my finals, I spent 2 months in hospital. Following those

2 months in hospital, I spent 8 months at home recuperating. I was completely reliant on my parents again. I couldn't even manage the walk to my bedroom; I waited another 2 months until I was fit enough for that.

Being 21 with long lines up my arm for IVs and on high doses of steroids meant that I lost all self-confidence and despite my school reputation became very insecure and unsure around men. The side effects of the drugs (particularly the steroids) took their toll and my entire body changed shape; my stomach and face swelled up, which made me dread any invitation to a 21st or any other party. On top of this, I was in constant fear of another relapse.

As time continued and my health strengthened, I managed to complete my physics degree; get a job; move to London; and even get a boyfriend, John.

After 2 years, he took me to India and proposed. My young fears of thinking that no one would even sleep with me due to CF were definitely completely unfounded. I couldn't believe how lucky I was. But did he know what he was really in for? Well, he soon learnt. Only 3 weeks after we got engaged, my long feared relapse came. On Christmas Day 2007, I fell ill. The next day I was in hospital again, which was where I remained for the following 5 weeks. I was on all the tubes and drugs that I was on 3 years earlier. I couldn't believe it. I didn't know whether to plan my funeral or my wedding.

My body started to change again and I started to not even want a wedding if I was going to look like I did last time. The support I received from my new fiancé shocked me into fighting again. He promised me that we were getting married even if I came up the isle in a wheel chair attached to oxygen, and if we needed to postpone our wedding day that was fine too. He spent every day he could with me and made me more and more determined to be myself again. And I did it! I had the wedding of my dreams.

After a few years of marital bliss, the thought of children started to enter my head; maybe I should say our heads. These ideas were shattered as the winter came and I got swine flu. A week later, my lungs "shut down." It was happening all over again, although this time it was worse. After weeks of lying in bed trying to recover, I slipped a disk by coughing and had sciatica and couldn't move my right foot, which really stopped any progress. My recovery was the hardest to date and I temporarily developed CF-related diabetes.

For 4 of the 7 weeks I was in hospital, I couldn't leave the room due to swine flu risks. Anyone who came into my isolation room had to wear gowns, gloves, and a mask, so not only did I not see even a human face for 4 weeks but when I did eventually leave my room I felt dizzy and faint as my eyes had not focused beyond the realms of my four walls. I had to start looking out the window more so that I could get used to the idea of the outside world.

The symptom of CF that I believe is the most universally hated is the clogging of the lungs with thick sticky mucus. I can't describe how hard it is to actually produce the mucus. It can cause me to break into a sweat, vomit (from refluxes),

and pull muscles. Physiotherapy and all the other daily requirements just to keep patients functioning can quite literally take all day.

Somehow I recovered from swine flu and the diabetes stopped as it was steroid induced, but I could feel that something else was not right. My lung function had improved back up to FEV<sub>1</sub> of 48% and FVC of 100%, but I could feel a block in my left upper lobe despite there being no signs on x-rays, computed tomography (CT) scans, or blood tests. I then started to cough small black dots. Over the months, these black balls (sometimes in sputum sometimes on their own) became bigger. Then one morning, I coughed up one the size of a pea. I caught this one in a sputum pot and took it straight to the hospital as I had an appointment that day. It turned out to be a ball of fungus called *scedosporium*. After many consultations, I was told that there was a sign of a fungal ball in my CT scan from back when I had swine flu. Well if this ball was still there, it was probably bigger now as what I was coughing up was bigger and I wasn't feeling better. I had a few large hemoptysis as well, where I had coughed up about a half to a pint of blood so I was definitely not improving but was doing my best to stay healthy.

Six months post swine flu, my lung function plummeted and I knew that this time I was not going to get better. I don't know if it was mind over matter or if I just knew my own body. Either way, I was going to fight every step of the way. This to me meant doing all my drugs and saying yes to every test, new drug, and whatever the doctors suggested; it meant doing my physio everyday and asking to go to the gym (even if on oxygen and being wheel-chaired there) and getting on an exercise bike everyday, which I did (and had done since I first got seriously ill 7 years prior).

I spent 3 weeks in hospital and managed to "escape" for my grandfather's funeral, at which I somehow managed to play the saxophone (sitting down) despite the fact that I could tell I needed oxygen. I had to lie down throughout his reception afterward. But I managed his request that I play at his funeral, so I was happy with that.

Two days later, I was due to be a bridesmaid and I managed it. My mother got me ready as I was so breathless I could not bath myself. I had help up and down the aisle by holding another bridesmaid's arm. I struggled to walk to the loo, but I was determined to be at my best friend's wedding. A few days later, I was in hospital with a mixture of relief and disappointment. Damn—I was on oxygen again, never to come off it. The block in my left lung was getting more and more uncomfortable. I still hoped I would improve like last time.

I went into hospital on August 11 and stayed there till December 24. In November, a new drug was going to be tried on me as I was a very "odd" case suffering from an allergic reaction to *scedosporium* (like ABPA), but my weight was good and the rest of me "worked." If this didn't work, then transplant may be an option. At the time, transplant seemed so terminal. I knew the odds and couldn't

believe I was already there. But I knew as things stood that was where I was heading. The drug was monthly, so I knew it was going to take time if I was to recover. But there was still hope and that was the main thing; there must always be hope.

After a few weeks, I remember saying to myself as I did my daily hike up the stairs to bed, "God, please give me a pair of new lungs." I knew then I needed a transplant. My body couldn't cope anymore. I wanted the relief of being looked after in hospital and that's never a good sign. Patients, I think, will all try and push it as long as possible, but we all know how much easier it is once we get into hospital and are looked after. In April, I became a permanent resident in hospital. It was then decided that I should be assessed for transplant. I was never certain how sure the previous two talks of transplant had been as the doctors clearly found it difficult to break it to me as well. I always liked the doctors who would come and sit down and look at me at my level and talk to me as an equal and not as an idiotic patient. I am an expert in my own body and have dealt with CF for longer than some of them have been alive. By the time I was told I would be assessed, I was relieved. I could tell I was declining fast and I felt there was, at last, hope again. Not everyone sees it like this, but this is the only way to look at it. It is a chance to live again.

In May, I had a night where I nearly died. An enormous fungal plug blocked my airways and I couldn't breathe. The nurses all rushed in as I called the normal call bell. I saw the concern in their faces as they called more help and ITU. Suddenly, this huge "pebble" came flying out of my mouth, but there was no relief. I just had to concentrate on every breath. The doctor called my husband who came in and saw me on NIV struggling to breathe. Seeing his face was horrid and I couldn't talk, but he just held my hand and begged me not to leave him and that he loved me. He was in tears and I was helpless. My mother came rushing down in the car from Cambridge to London and arrived later once things were calming down. ITU decided not to take me but considered ventilating me at one point. That shocked me as I knew that if I was ventilated I wasn't coming back. At least that's how I felt, despite what I was told.

My consultant came to see me first thing and looked very concerned and later told me the next few days were touch and go and I was moved to a high dependency room. I was very quickly assessed for transplant. I heard of a guy not getting on the list because he did not weigh enough. I felt like that would be a death sentence, so I begged, hoped, and prayed that I would get on the list. At the time, this seemed like the biggest, most important challenge. I could be prodded, poked, whatever (and I was), I just wanted to get on that list. I was told on June 15, 2012 that I was going to be accepted. There were celebrations all round. I knew the odds, but at last I was on the list; I had done all I could. Now I just had to stay alive and hope that I got that call.

While waiting for a transplant, my friends and family kept me going. It was never spelt out to me how ill I was

until I asked. The fungal plugs were getting bigger and more frequent and it was getting harder and harder to breathe through. I knew I didn't have long left. I was giving myself until September in my head.

Days after my birthday in late July, I had my hardest fungal plug and thank goodness the physio was there to talk me through it and talk me through the breathing. I think it saved my life. I realized that I was a scary sight even for doctors. I just didn't want to be the next death on the ward; I wanted to be a success.

A week after my birthday, the nurse walked into my room and said "Emily." I knew immediately by her smile what was coming. It was the call. Then she said that Harefield had some possible lungs. This was it. Mum and a friend were with me. They grabbed each other as my phone rang. And the conversation is a bit of a blur, but all I remember saying is "yes, please" a lot. Then it was all systems go. I paid my credit card bills as I knew that if anything went wrong I had to be prepared. I declared on Facebook I was off to Harefield as I had promised my friends I would. Everything got thrown into a bag. My favorite junior doctor came and said goodbye and good luck with a huge grin on his face. The nurses hugged me goodbye. They had all become my friends over the last year. I could feel their emotions, but mine was excitement and relief as that week I had been getting worse. This was it; please don't be a false call. It was 6 weeks since I had been put on the list, so I knew that statistically it could be a false call.

My only problem was that my husband had gone away after much persuasion to take a break. So he was in Africa. He had decided to go to an island off the coast of Kenya just for the night, and obviously it was that night! I finally got hold of him and he wanted to know whether to fly back. If this was just a false call, he could come back for nothing. So I decided that he should stay put.

As I arrived at Harefield Hospital, the transplant coordinator told me she had "high hopes for these lungs." I was washed, with my mother's help, in pink chlorhexidine from head to toe and waited to hear if it was going to go ahead. Although you have thought about every aspect of what it means to have a transplant, and that someone has to die for you to live, it is still difficult at the time wishing that when the ventilator is turned off the person dies quick enough for you to get their organs. I had a nonbreathing donor, that's all I knew. I was told at 01:15 that the operation would go ahead. I had been kept informed every step of the way and felt in safe hands. I knew I did not have much left in me and was so happy to hear it was finally happening.

I called my husband who was so upset he wasn't there, but then again saying goodbye to him was hard enough on the phone let alone doing it face to face. For that reason, I was glad it was only my mother on that night. She had kept me alive, and this was her achievement as much as my own and my husband's and all the other supporters I had had physically and emotionally. I hugged her and told her she was the best mother I could ever hope for; she was my rock.

I woke up feeling groggy but with no NIV, which I had been using since that night in May. I was annoyed that no one was with me; I had woken up Thursday evening at 8:30 pm, which is after visiting hours. I then chatted all night, high as a kite, poor nurses. Friday morning came and in came Mum and Dad with huge grins. All was well. Then my mother-in-law came in and we all just held hands. My husband was on his way and arrived what felt like minutes later. My vocal chords were damaged, and I couldn't talk properly for weeks/months, lucky John.

Later on, I got extremely frustrated with the lack of communication I had with the doctors. I feel it is essential for doctors to communicate every step of the way with patients. It helps with panic attacks as everyone panics when they get that ill. I definitely panicked before my transplant at times, but the doctors always made me feel better like no one else could. They are the ones with the ability to prescribe medication and make decisions. So it is them who can change things. They are playing God. The lack of communication made me wonder how I was doing and what was going to happen. The weekly ward round is very impersonal; it always has been and a patient will never (I have never heard of one) open up in front of a room full of strangers, half of whom you have never seen and to whom you are just another statistic, or so it feels. The time the consultant came and sat in a chair for 5 minutes made all the difference to my stay and I could relax and then finally ask all my questions. I always kept a list of questions.

My husband cried the first time I walked outside, and suddenly the idea of a normal life crept on me as I got stronger and started to walk, shower, and climb stairs, none of which I had done in months/years without help.

I finally was allowed to say hello to home again. A place I had said goodbye to, thinking it was unlikely I would ever see it again. Then it was home sweet home. I was suddenly down to two very quick nebulizers every day, but compared to what I was on that was (and is) nothing and I have time in the day!

The best thing I noticed was the mornings. I could now spring out of bed and have energy straight away, instead of feeling all the rubbish in my lungs and not being able to move. I can walk my dog, watch Harry (my little brother) play Rugby, and do things I hadn't in ages. Everything was new again and exciting. Lung function was increasing all the time, and I couldn't believe it. I saw my lungs increasing in size on the x-rays. Hospital visits decreased very quickly over the following months, and suddenly I had a life again.

The only sad part is that I can't be around my other brother Ed, the one with CF and so can't see him, but thank God for Skype. I did see him the other day, but we both wore masks.

I keep pinching myself; this has all actually happened. I feel like I have won the lottery. There is not anything that can prepare you for some of the torture you are put through, but, wow, it is worth it and who knows what the future now holds. It's like my grandmother always said, whatever happens, "Life goes on."

## PARENTAL VIEW

RUPERT AND FRANCES PEARCE GOULD

### BEGINNING

In 1984, our daughter Emily was born. Within 2 to 3 days, she was breast-feeding voraciously on demand. This was followed almost immediately by an explosive movement of lime green stools. Despite this, we were sent home and told that babies sometimes produced green stools and not to worry.

At the 6-weeks checkup, our competent GP referred Emily to a pediatric clinic at the Westminster Hospital, where she was diagnosed with CF using the sweat test. We were asked if there was a history of similar problems in either family and Rupert recalled his younger brother died at 18 months, of “pneumonia.” He spoke to his mother and it became apparent that, whereas death was from pneumonia, in fact his younger brother suffered from CF.

Emily was referred to the Brompton Hospital where the consultant gave us an honest, blunt talk on CF and the prognosis, followed by the fact that treatments were improving every day and that with luck and good management she could survive beyond 21 years. Twenty-one years seemed a long way away and yet such a short life.

The talk helped us look to the future with reality and determination, and we were determined that we would do everything to ensure Emily would live as long and as normally as possible. In short, we had a mission in life! We were visited by a family friend (an adult CF consultant) who talked at length with both of us and gave us a greater sense of optimism for the future. His visit and talk was both comforting and reassuring.

Exhausted from all the feeds, Frances set about mixing pancreatic powder (pre-Creon pills) with a bit of expressed milk, which was spooned into Emily’s mouth.

We also had to start the routine of physiotherapy on the lungs—postural drainage and gently percussing her chest with cupped hands. We taught grandparents and, later on, au pairs how to do the physio twice a day. Later on, she would tell us how to do it most effectively and with the least discomfort.

Tiredness and anxiety were constant feelings in those early days, no less so than when Emily was admitted to hospital at 5 months with *Pseudomonas* for a course of IV antibiotics. The existence of a CF nurse specialist to refer to in the hospital was a great help: someone who was always around, to form a relationship with, and to whom we could voice any concerns.

We were enjoying Emily, and we would have liked a family of more than one but realized that there was a one in four chance of having another CF child. At this point, the CF gene had not been isolated, but an early form of antenatal diagnosis was on offer if we wanted to take the risk.

### CLOCK STRIKES TWICE

So we decided to try for a second child. Antenatal diagnosis gave us the all clear, which was a relief, and our son Edward was almost born early (in the Majestic Wine car park) some 22 months after Emily.

Unfortunately, within 3 days of his birth Frances was certain that Edward was suffering from CF as he had the same explosive green stools. This was confirmed by the Brompton Hospital a few days later with a sweat test (no DNA test in 1986), and he started taking Creon with his feed straight away, to good effect.

After the initial shock, we decided that we had no choice but to resolve to bring our two CF children up as normally as possible and give them the best chance of survival that we could.

So now we had two children only 22 months apart both with CF. (For the record, some 10 years later we had a third child—screening was better, and he does not have CF.) Having two was not quite double the problem, but it certainly created a strain and there was no way of shortening the time taken to complete the daily routine of physiotherapy and nebulizers.

### FAMILY AND FRIENDS

Through the Cystic Fibrosis Trust, we met others who had the same problem, many of whom are still friends today despite having their own trials and tribulations. This was an amazing sense of comfort, and we are eternally grateful to them for all their words of guidance and advice and we were able to build on their experiences and their own optimism for the future.

We had great support from the family. Of course, on Rupert’s side we had two “grandparents” who were both carriers and had experience of a child with CF, albeit very briefly. On the other, only one grandparent is a carrier and with a rare mutation.

### ADOLESCENCE

When do children grow up? It was our CF nurse Jackie who spotted Edward, aged 15 with a school friend in the pediatric clinic, reading an adult male magazine while younger children with CF were running around with toys and watching Walt Disney. Jackie announced, with amusement, that it was high time for him to move to the adult clinic and join his sister.

At 11 years of age, Emily decided to keep her condition a secret at her new school and instructed Frances not to tell anyone that she had CF. On her first day there, Frances disobeyed her and quietly slipped a pot of Creon pills into the hands of her form mistress should the day arrive when she may forget to bring them into school. That day inevitably arrived, and she was forgiven for letting her teacher know by which time she had selectively told her closer friends about her condition. The same happened when Emily went

away to school in the sixth form and her housemistress organized for her to have a separate room to keep all her medication and nebulizers. Only the matron and very close friends knew about her condition. She even kept it from a serious boyfriend for over a year and then consulted with Rupert about whether she ought to tell him.

Edward, on the other hand, was more laid back about his CF and didn't seem to mind people knowing about it. However, that attitude belied the fact that as a teenager he became angry and frustrated with the daily routine of physiotherapy and nebulizers leading to the occasional outburst at school. He was not as open with us about his condition and thought about it a lot more and was no doubt considering the reality of a shortened life expectancy. We think he bottled things up more... If he asked a question about his condition, he only wanted a direct answer and then switched off if we tried to elaborate; he wanted facts. So different from Emily, who wanted to talk about everything.

At this stage, the CF patient has a changing attitude to life. In particular, girls become sensitive of their changing bodies and Dad's offer of physio may well be rejected. Nothing we believe to do with Dad but all to do with the changing body and maturing attitude.

Boys have their own issue, and one has to judge when is the best time to tell him that his fertility has been affected by CF and that he may be sterile.

We were amazed at how much Edward did understand. The consultant who was helping to explain to Edward that he would be sterile was knocked back a bit when at 10 years of age Edward asked, "Good—does that mean that I do not have to use condoms?"

Both our children went on to university, and living away from home was a major point of transition to adulthood. Flatmates and so on were helpful, but they had normal lives and their socializing was indeed a distraction to maintaining a good regime. It seems that all young adults test their bodies, and in this respect a CF adolescent is no different. However, in our case there were other telltale signs that they had overdone it, but we had to learn the art of judgment as to when to say something and when to let them find out for themselves.

Just before her finals at Bristol University, Emily had her first bad bout of flu leading to 3 months in hospital on oxygen and with her resistance being low she caught a secondary virus in hospital. Our lives became geared toward daily visiting at the Brompton Hospital and juggling with two other children (by then, we had another son of 8 years, who does not suffer from CF). During Emily's stay in Brompton, we were reminded of the seriousness of her disease when she had one or two frightening moments and we wondered whether she would ever get better.

She recovered and Bristol University agreed to postpone her finals to the following year. In the meantime, she found a good job in PR based in London. Following her finals, she decided to move to Abu Dhabi to be with her boyfriend (who she went on to marry).

Edward went off to university and managed to keep quite well, playing a lot of sport and bicycling to lectures.

By this time, the adult CF child is in control and we had to remember that Mum and Dad cannot continue to monitor their children and are not in control. So our advice is to ensure that good friends and colleagues have your mobile phone number so that if there is an emergency you can respond and get help. In fact, we were called upon and had to leap into action to provide the support, comfort, and warmth plus of course good food and so on.

When they move away from home, they are beginning to understand the limitations and probably now know their bodies better than their parents. That telling comment from Emily to Rupert "how do you know what it is like—you don't have CF?"

## ADULTHOOD

Moving on from university means that the real world is looming and today the future even for CF patients is opening up much more so than when our children were born.

Emily is now happily married. This was a joyous occasion, but one does wonder whether they have chosen a partner who will stay with them on the journey through the most difficult part of their lives. At this stage, our children looked perfectly normal, but explaining the ticking time bomb to a potential partner and what that may entail needs a lot of support. Luckily, Emily chose well and has a fantastic marriage with a loving husband who fully understands the issues and is very supportive.

Another bout of illness followed while she was first engaged and was home for Christmas (winter time is never good). Yet again, there followed 3 months in hospital with a worried fiancé John who flew back to England from Abu Dhabi to see her. The support was needed not just for Emily but reassurance and optimism was needed for John. We worried that he may find it difficult to accept the downside of her disease; at the time, we thought it was perhaps a good thing that he understood what he was taking on. It was a great relief that he still wanted to marry her despite the difficulties that lay ahead.

Emily's decline coincided with a bout of swine flu at the same time as their much loved maternal grandfather was dying. Frances was pulled in all directions, and it was difficult for her to give the two other children (one with CF) much attention.

Edward was fit enough to be able to run the London Marathon and we all went to support him. We were so proud of him. He then went on to do a triathlon, the Great North British Swim, and a Cardiff Half Marathon.

In adulthood, key issues start to emerge. Are CF patients going to have normal careers? Will they get married? Will they have children? All of this with a limited life expectancy hanging over them.

We have always considered that our CF children are the same as any other child and therefore a purpose in life is important. What that purpose is will depend on the individual.

## TRANSPLANT

Just as her maternal grandfather died, Emily went into hospital and stayed there for much of the following year culminating in being accepted on the lung transplant list in June 2012. Transplant had not been something we had talked about until the numerous antifungal drugs were failing to make any impact. We had always considered it as a last ditch treatment; but we found ourselves wanting a transplant for Emily more than anything else, especially as it dawned on us that the clinicians were running out of pharmaceutical remedies.

As she was being assessed for transplant, we began to come to terms with the fact that time could be running out. For us, it was a relief that a decision had been made after months of struggling with treatments that were unable to stop the onslaught of fungus in her lungs. For friends, it was a shock as they either didn't realize she was so ill or had been in denial about it.

Keeping positive and keeping going was all that mattered. As time moved on and her condition deteriorated Frances had to have conversations any mother would hope never to have with her daughter, but she needed to be able to discuss what might happen should she not survive. It was hard for both of us, but at the same time she never gave up hope of having a transplant.

For Rupert, there were the pragmatic concerns of what about John, and what about wills, and so on. Emily was, as ever, down to earth and took it all head on. In fact, at times she seemed to be comfortable in hospital and had small parties of friends in her room. This was interspersed with regular visits to the prayer sessions on Sunday.

Her determination to get on the transplant list was apparent in the way she badgered the doctors to book all the medical tests and assessments required, to be accepted on the transplant list. We didn't want to do anything but support her and be there for her whenever John couldn't be.

Following a frightening episode when Emily's airways became blocked with a plug of mucous, preventing her from breathing, we all took turns to spend the night in her room so that she would never be alone. Frances will always remember the late evenings walking Emily through the ward carrying her oxygen for her and chatting to the nurses. Rupert had some lovely evenings trying to beat Emily at backgammon, and John spent many nights with her after work. Like so many in the ward, she was struggling to breathe; it was a worrying time for all of us.

Both John and Rupert had full-time jobs to juggle with and mix with spending evenings, if not all night, with her. Fortunately, Emily was self-driven and always determined and always cheerful, accepting what life was throwing at her.

Edward visited occasionally but was extremely careful and wore a mask to protect himself as well as Emily. Her younger brother Harry visited when he could, as he was away at school. Support from John and a devoted group of

friends helped us through this time with moments of fun and humor. We bought her a Dyson fan during the summer, which was a lot quieter at night. Sharing the care with John made it easier, although he needed support as well. He was trying to keep a job going and spending time with Emily.

When the call for a transplant finally came, Emily was relieved and excited. Edward was more openly worried the night of the transplant and called Frances several times during the operation clearly frightened. She had to reassure him that the operation itself had a very high success rate. For him, the experience must have been frightening, as he contemplated his own future and the fear of losing the only person in the family who really understood his condition, could give him good advice, and understand exactly how he felt.

It was probably easier for Frances as she was totally involved in traveling with Emily in the ambulance to Harefield and sharing the excitement and the anticipation with her. Phone calls to close family had to be made, especially to John, who was abroad with his father having a well-earned break, and Rupert, who was in the middle of a difficult meeting. None of us imagined that a match would be found after only 6 weeks on the transplant list. Emily was the most optimistic of us all.

Fortunately, there was a sense of calm and some humor as Frances helped her to prepare for theater and waited to hear whether the donor's lungs were good enough for transplant. There was a sense of excitement as Frances accompanied her to theater. She confesses to having shed a tear as she hugged Emily when she said goodbye in the theater; her parting words were, "I will see you in ITU in a few hours." Rupert had no choice but to snatch some sleep for the challenge of Thursday morning whatever that would entail, and who knew?

As we walked into ITU to see Emily looking beautiful and calm on a ventilator, there was a huge sense of relief that she had reached this stage and gratitude to the poor donor and their family and all the medical effort that had got us to this point. This must have been reflected in the many e-mail texts sent and telephone calls we made over the next few weeks. John set up a Facebook page so that the many well-wishers were kept informed as access to Emily was restricted.

Our outlook changed as Emily made a good recovery over the next few weeks despite a brief setback when she contracted pneumonia. Rupert visibly relaxed more and enjoyed visiting her in hospital, watching more of the Olympics than intended.

Although we saw very little of Edward over this period (as he was not allowed to come and visit Emily), we spoke to him often. We often worried about how he coped with the year when she became so ill and he was not able to visit much, but luckily he had a very supportive girlfriend; we encouraged him to take time off and do some traveling while he was well enough. We are sure that at that time he considered this his last possible time for long-distance travel as he had seen the difficulty Emily had had with travel. Although