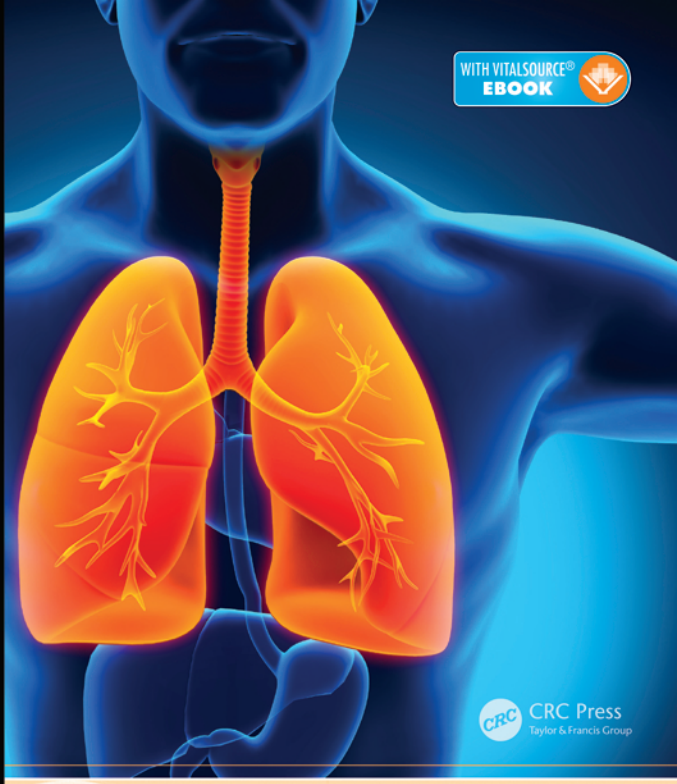

FOURTH EDITION

Hodson and Geddes' Cystic Fibrosis

EDITED BY
Andrew Bush • Diana Bilton
Margaret Hodson

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Preface

"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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PART 1

Introduction: What is cystic fibrosis?

1

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

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

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

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.[1] 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

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 *CFTR* 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	Collins FS, Riordan J, Tsui L-C
	Advances in medical treatment of cystic fibrosis	Rosenstein BJ
	A look toward the future	Boucher RC, Wilson JM
1990	The CF gene one year later	Collins FS, Riordan J, Tsui L-C
	Gene therapy and model systems	Caskey CT, Crystal RG
	Immunopathology and new approaches to therapy	Berger M, Hoiby N, Moss R, Suter S
1991	The CF gene two years later: Progress and projections	Collins FS
	New frontiers in therapy	Crystal RG
1992	The CF gene: Perceptions, puzzles and promises	Collins FS
	The new pharmacology: Tools to arrest CF lung disease	Boucher RC
	Gene therapy in CF: Progress and prognosis:	
	In vivo gene transfer strategies for the respiratory manifestations of cystic fibrosis	Crystal RG
	Strategies for gene therapy of CF	Wilson JM
1993	The CF gene: Old questions, new insights	Collins FS
	CF: Electrolyte transport revisited	Welsh MJ
	Gene therapy for CF: A glimpse into the future	Boucher RC, Crystal RC, Whitsett JA, Wilson JM
1994	Understanding cystic fibrosis: Accomplishments and challenges on the road to a cure	Welsh MJ
	Advances in clinical science and management	Davis PB
	Prospects for human gene therapy of cystic fibrosis	Wilson JM
1995	1995: The year in review	Collins FS
	Clinical advances in CF: Recognizing the cure	Davis PB
	Human gene therapy for CF: Lessons learned & hurdles to success	Crystal RG
1996	CF research: Highlights of 1996	Collins FS
	The immune system: The devil within of the good guy?	Wilson CB
	On track with CF gene delivery vehicles	Wilson JM
1997	CF research: The best of 1997	Collins FS
	New clinical developments in CF: From the test tube to the bedside	Ramsey BW
	Gene therapy for CF: Where have we been and where are we going?	Crystal RG
1998	The best of 1998	Taussig LM, Tsui LC
	CFTR structure & function: pathophysiologic insights & novel targets for pharmacotherapies	Guggino WB, Hanrahan JW
	The CF cure: How close are we?	Cantin AM, Davis PB
1999	The best of 1999	Boucher RC
	The process of drug discovery—an enlightened journey	Beall RJ, Campbell PW
	New clinical interventions	Ramsey BW
2000	The best of 2000	Wine JJ
	CFF mission and vision	Beall RJ, Campbell PW
	Solving the puzzle: CF clinical research 2000	Accurso FJ
2001	The best of 2001	Welsh MJ
	Why won't they do what we tell them to do? Understanding families and understanding adherence	Bluebond-Langner Myra, Lask B
	CF clinical research: A journey with a destination	Cantin AM
2002	CF airways pathophysiology: CFTR & beyond	Boucher RC
	Changes in the natural history of CF from a GI perspective	Durie PR
	Developing better therapies for patients with CF: 2002 Progress report	Ramsey BW
2003	From genes to drugs: The CF master plan	Collins, Beall RJ, Ashlock MA
	Providing exemplary care: A partnership for change	O'Connor, Marshall BC
	Disease progression in CF: Can we gain the upper hand?	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	Davis PB, Konstan MW
	How do we recognize a clinically effective new treatment?	Alton E
	Care providers and people with CF: Together we can make great things happen!	Batalden P, Acton JD, Page HO
2005	50 years of CF: Milestones to a cure	Campbell PW, Beall RJ
	50 Years of CF clinical trials research: Accelerating the progress	Goss CH
	CF nutrition: Opportunities for the scientist & the care team	Borowitz D
2006	Promises to keep: Turning discoveries into drugs	Davis PB
	Clinical research: Our compass to a cure	Clancy JP
	CF pulmonary care: Measuring & improving our effectiveness	Yankaskas JR
2007	From basic science to the clinic: Where are we and what is still missing?	Amaral MD
	CF drug development: What's new?	Ratjen F
	Improving patient outcomes using the tools we have now	Boyle MP
2008	Preventing CF lung disease	Wine JJ
	The CFF pipeline: The amazing story of progress, hope, and challenge	Campbell PW
	Taking the CF battle to the extremes: Healthy starts with newborn screening; healthy aging with improved adult care	Farrell PM, Simon RH
2009	Two decades of CFTR research: From gene discovery to therapeutic target	Collins FS, Rowe SM
	Inflammation & infection: Update on the pipeline	Konstan MW
	Early airway infection in young children with CF—what is the optimal therapy?	Ramsey BW, Retsch-Bogart G, Wainwright CE
2010	Pipeline: Airway surface liquid modulation	Sorscher E
	Animal models	Stolz DA
	Transforming CF healthcare: Partnership for life	Berwick D, Marshall BC
2011	CFTR modulation—25 years of NACFC progress	Mall MA
	CFTR 2—a research & clinical practice tool	Cutting GR, Sosnay P
	Pulmonary exacerbations	Flume PA
2012	Reversing the basic defect: A vision for the future	Rowe SM, Skach W
	Advances in GI aspects of CF	Borowitz D
	Adherence … Where's the app for that?	Riekert KA
2013	Restoring CFTR Function: Roadmap to a Cure (Part 1)	Donaldson SH
	Roadmap to a Cure (Part 2) Clinical Research Pathway to Ensure That All Patients With CF Benefit From Novel Therapies	Ramsey BW Engelhardt JF
	CFRD: From Bench to Bedside & Back Again (Care)	Kelly A
2014	Scaling the Mountain: The Journey to Delivering Transformational CF Therapeutics	Boyle M
	CF Microbiology Past, Present, Future	LiPuma J
	CF Advisory Board Track: From Codman to Collaboratories: A Care Model for CF That's Fit for the Future	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

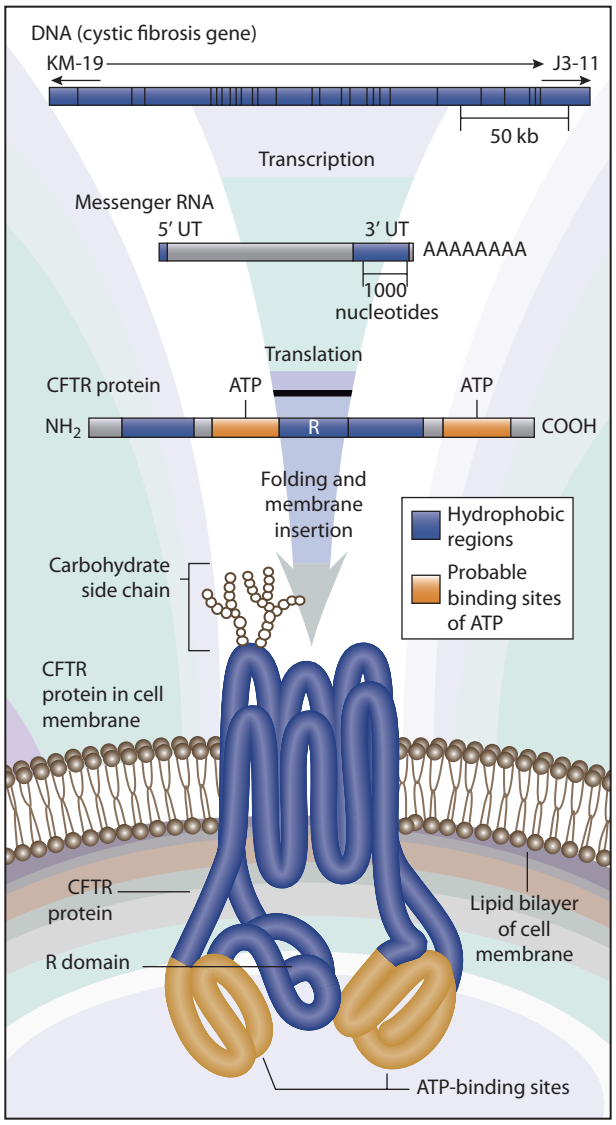

Figure 1.1 Early cartoon depicting the different domains of the cystic fibrosis transmembrane conductance regulator protein.

paradigm has remained 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.[2,3] 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.[4–6]

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 downregulation by blockers such as amiloride. But the first clinical trial failed, the failure being attributed to amiloride's short-lived action.[7] Although, in recent years, the CF pig model questions the theory of ENaC hyperactivity,[8] 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 β-ENaC overexpressing mouse model deserves specific mention.[9] 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.[10] 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. Denufosol, 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.[11,12] In the mean time, these alternative chloride channels have been nailed down as the TMEM16A proteins.[13]

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.[14] 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.[15] We learned

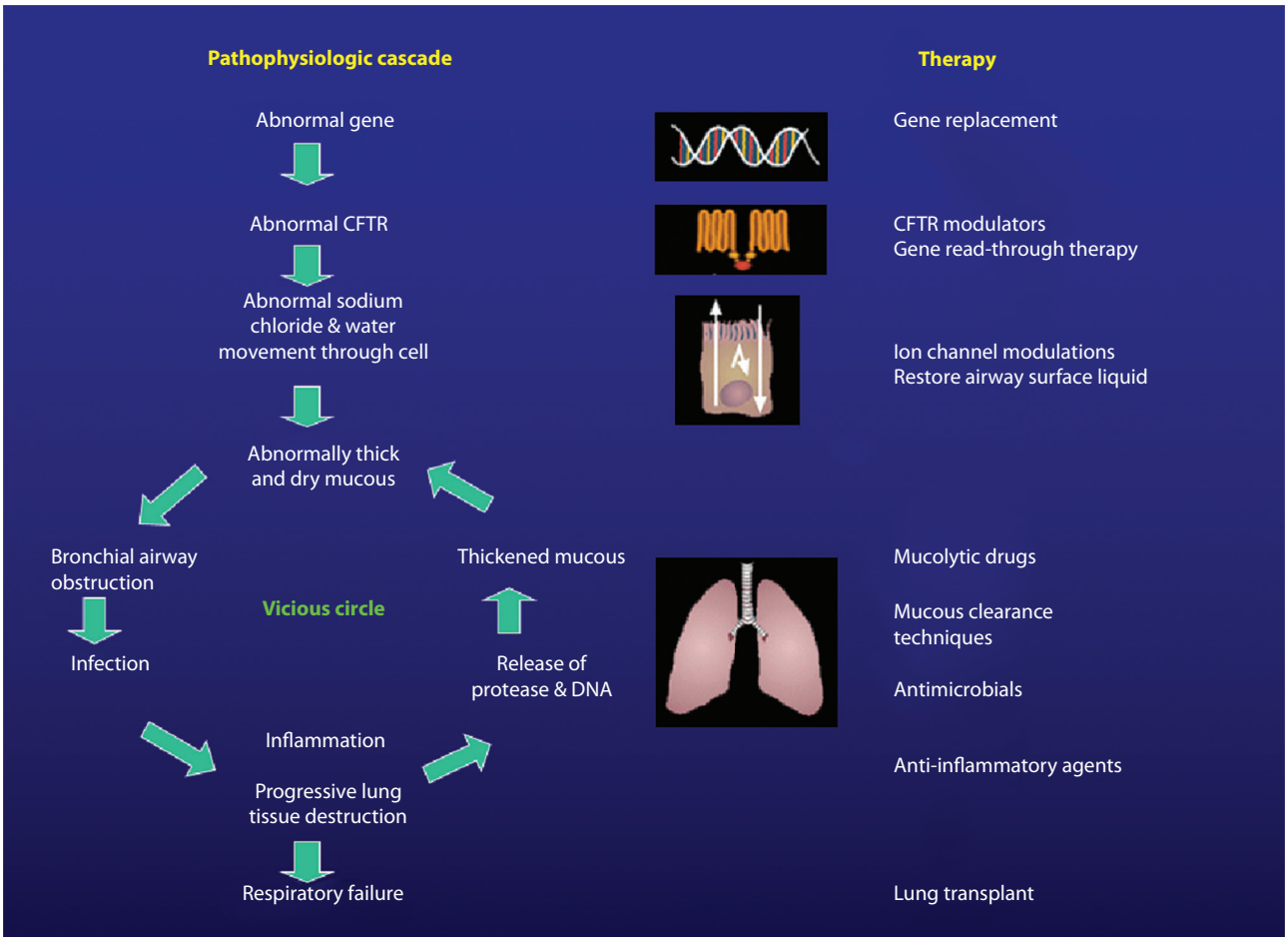

Figure 1.2 Paradigm of cystic fibrosis pathophysiology plus listing of putative and existing therapies to improve or prevent lung disease.

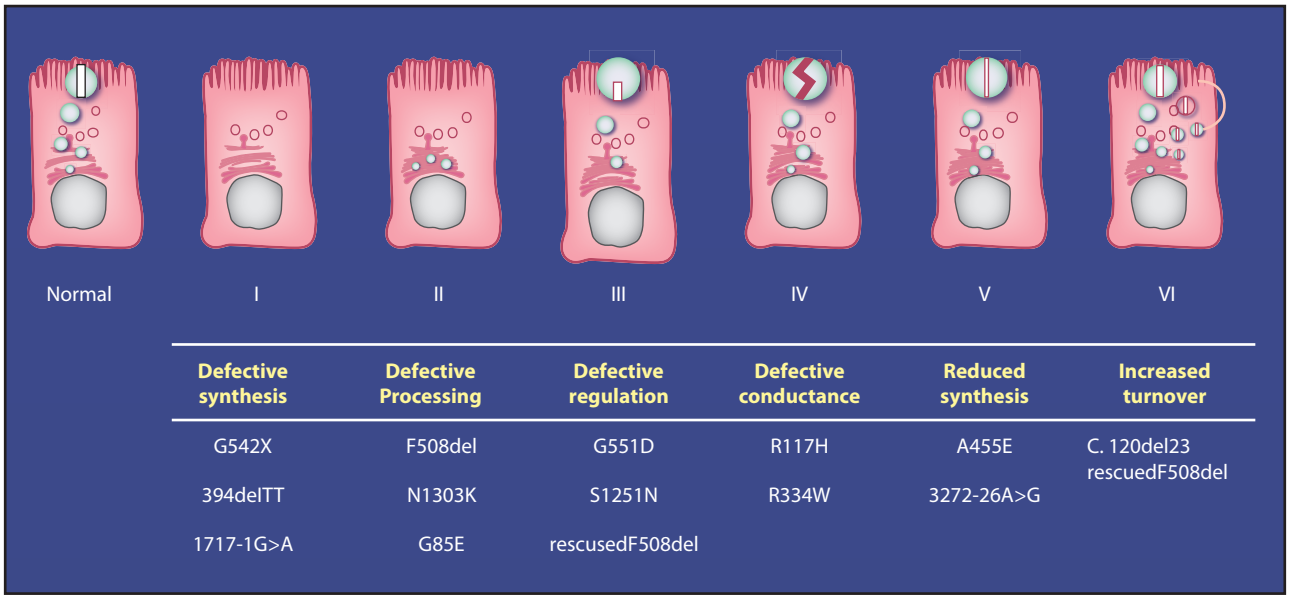

Figure 1.3 Cystic fibrosis transmembrane conductance regulator (*CFTR*) mutations are grouped in classes according to how the *CFTR* mutation interferes with CFTR protein synthesis or function. (Adapted from Amaral, M, and CM Farinha, *Curr Pharm Des*, 19(19), 3497–508, 2013.)

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.[16,17] Different groups uncovered several modifier genes, but in later years genome-wide association studies were performed.[18] 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.[19] 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.

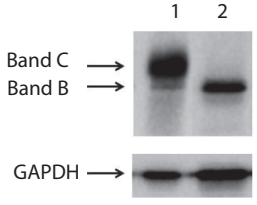

Figure 1.4 Western blot of cystic fibrosis transmembrane conductance regulator (CFTR) protein. Western blot of wild type (left) and *F508del* (right) CFTR protein expressed in BHK cells. In wild-type CFTR expressing cells, a prominent upper band, also called band C (corresponding to the fully glycosylated 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.[20] 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.[21]

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).[22,23] 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.[6] 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.[24] 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.[25–27] 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.[26,28] In the phase 3 clinical trial the primary outcome of improvement in FEV1 was not reached.[29]

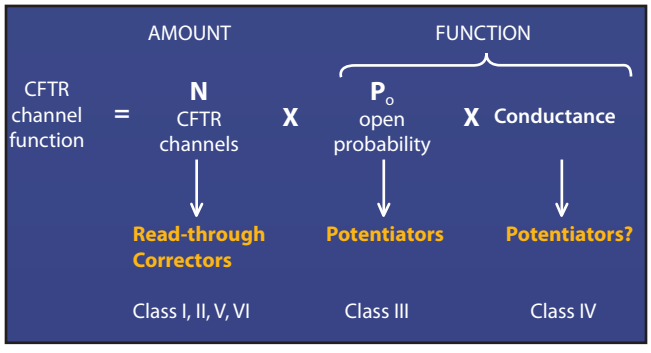

Figure 1.5 Current paradigm linking defects in cystic fibrosis transmembrane conductance regulator (CFTR) protein function or synthesis and *CFTR* mutation classes with potential therapies by CFTR modulators.

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.[30] The CF pig becomes infected with a myriad of bacteria,[31] has abnormal airway cartilage,[32] and has a disturbed growth hormone axis.[33] 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.[34] 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.[35] 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.[36–38] 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.[37] 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) 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.[39]

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.[40] 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.[41,42] 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.[43] A three-tier algorithm with IRT, DNA, and pancreas-associated protein greatly reduces detection of carriers and can also be considered.[44]

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.[45] And what to do with babies who are screen positive but have an equivocal diagnosis of CF?[46] Do they truly deserve the strange name of "CFTR-related metabolic syndrome" chosen on the other side of the Atlantic?[47] And, although CF screening uses excellent and increasingly sophisticated methods, they are screening and not diagnostic tests.[48] 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.[49] A good example of a large-scale CF trial of the modern era was the study of the efficacy of rhDNase.[50]

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.[51] 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.[52–55] 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) 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) 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.[56]

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_1) was no longer an easy to use surrogate outcome parameter.[57,58] 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.[59] Lung clearance index, a parameter of gas mixing efficiency, more sensitive than routine spirometry, was introduced in the field of CF by Per Gustafsson.[60] 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.[61] To better study the first steps in CF lung disease, the in vivo study of mucociliary clearance was also reenergized.[62]

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.[63,64] 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.[65] 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 consensuses 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.[65–70] Equally successful consensus conferences were held at Lake Garda, organized by Carlo Castellani, with a focus on *CFTR* mutation analysis,[71] CF NBS,[36] and carrier screening.[72]

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_1 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.[73] Airway inflammation and infection start very early in life.[74] 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,[75] 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.[76] 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.[70] 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%.[77,78]

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.[79] 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*.[80,81]

Systematic study of the lung microbiota taught that even the normal lung is not sterile.[82] The lung microbiota in CF is infinitely complex with a very vast spectrum of potential pathogens including countless anaerobic bacteria.[83] With increasing patient illness, the diversity of lung microbiota decreases.[84] 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.[85–87]

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.[88–91] 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.[92,93]

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.[94]

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.[95] 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). 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.[96] 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.[97]

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 financer 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

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,[1] Cystic Fibrosis Trust in the United Kingdom,[2] Cystic Fibrosis Canada,[3] and 2008–2009 data from the European CF Society.[4] We also included 2009 data from Australia published by Bell et al.[5] 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

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.[6] 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.[43] 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[a]

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][b]	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[a]

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 2000	2,714 3,608	Based on a study of temporal trends in CF birth prevalences
Canada—Saguenay-Lac-St.-Jean (Quebec) [37][c]	902	Based on data between 1975 and 1988
United States [38] Whites Non-whites	 3,419 12,163	Using national registry data between 1989 and 1991 and statistical models to account for underdiagnosis due to death prior to diagnosis
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.

[a] Expressed as the number of live births per incident case of CF.

[b] 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.

[c] 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.[44] 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.[36] In Victoria, Australia, researchers noted a decline in the live-birth prevalence of CF after the implementation of newborn screening,[45] and in Massachusetts researchers observed fewer children than expected identified with CF through newborn screening in 2003 through to 2006.[46] 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.[46]

In Brittany, France, where CF is relatively common (1:2948)[42] 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.[47] 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.[17] 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,[4] 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.[12] 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.[2] Similar trends emerge from US data from 2006.[2]

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%).[54]

Whereas *F508del* proved to be common, striking between- and within-country differences have been observed. Bobadilla et al.[55] 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+1G->T* in African-Americans; *621+1G->T* in Lac St. Jean; *R1162X* in US Native Americans; and *3849+10KbC->T* in US Hispanics.[55] 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.[56] 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_1), body mass index (BMI), pseudomonas infection, or pancreatic sufficiency.[57] Similarly, de Garcia et al.[58] 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[59] 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[a]	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[a]	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[a]	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[a]	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[a]	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[a]	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[a]	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[a]	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]

[a] 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.[50,60] 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[1] and 12 per 1000 in the United Kingdom[2] and in Canada.[3]

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.[61] 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[62] 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[63] 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.[64] 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.[65] In Australia, the mean age at death increased from 13.3 years in 1979 to 26.6 years in 2005.[66]

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,[1] 26.0 years in the United Kingdom,[2] 34.0 years in Canada,[3] and 25.0 years across Europe.[4]

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.[67] Current survival has been estimated to be 37.7 years in Italy[68] and 50.6 for males and 43.2 years in females in Canada.[3] 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[1] and 41.5 years in the latter.[2]

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.,[69] 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.[70] A separate study in the United Kingdom also noted improvements with successive birth cohorts when studying 3-year cohorts between 1968 and 1994.[26]

Being able to provide patients and their families with meaningful estimates of survival is important. Dodge[26] 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[1] are 18 years of age and older compared to 49% in Australia,[5] 57.2% in Canada,[3] and 48% across Europe.[4] 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.[71] 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.

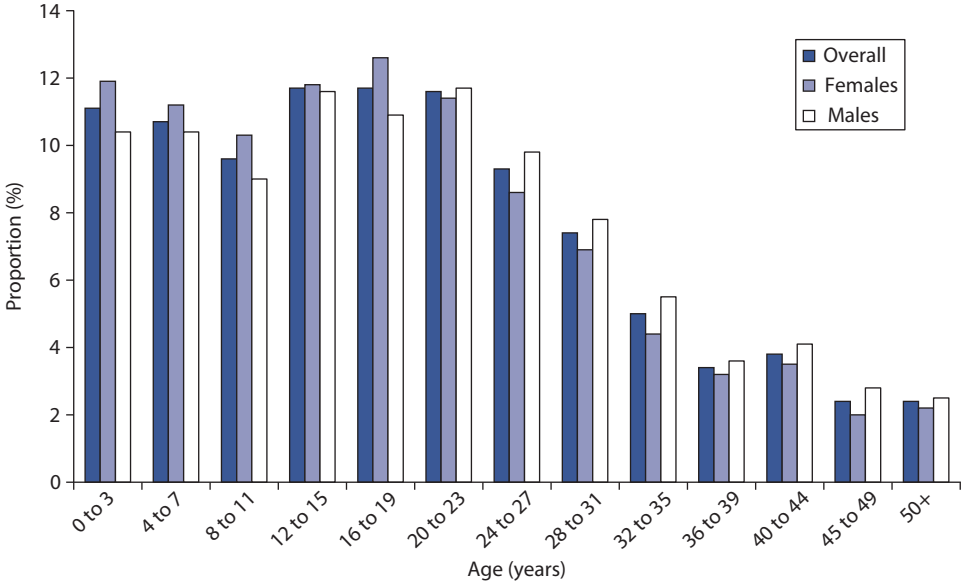

Figure 2.1 Age distribution of patients with cystic fibrosis seen at specialist centers in the United Kingdom in 2011. (From CF Trust, *Cystic Fibrosis Trust Annual Data Report 2011*, 2013.)

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[72,73] (see Chapter 25). In 2011, 8.6% of patients seen in the United Kingdom were 40 years and older.[2] Studying a cohort of these long-term survivors at a specialist adult clinic in the United Kingdom,[74] researchers noted that although these patients were less likely to be pancreatic insufficient and less likely to be homozygous *F508dt* 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.[72]

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.[75] 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,[1] 7 months in Canada,[3] and 3 months in the United Kingdom.[2] 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.[4] 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.[75] 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,[5] whereas in the United States this figure

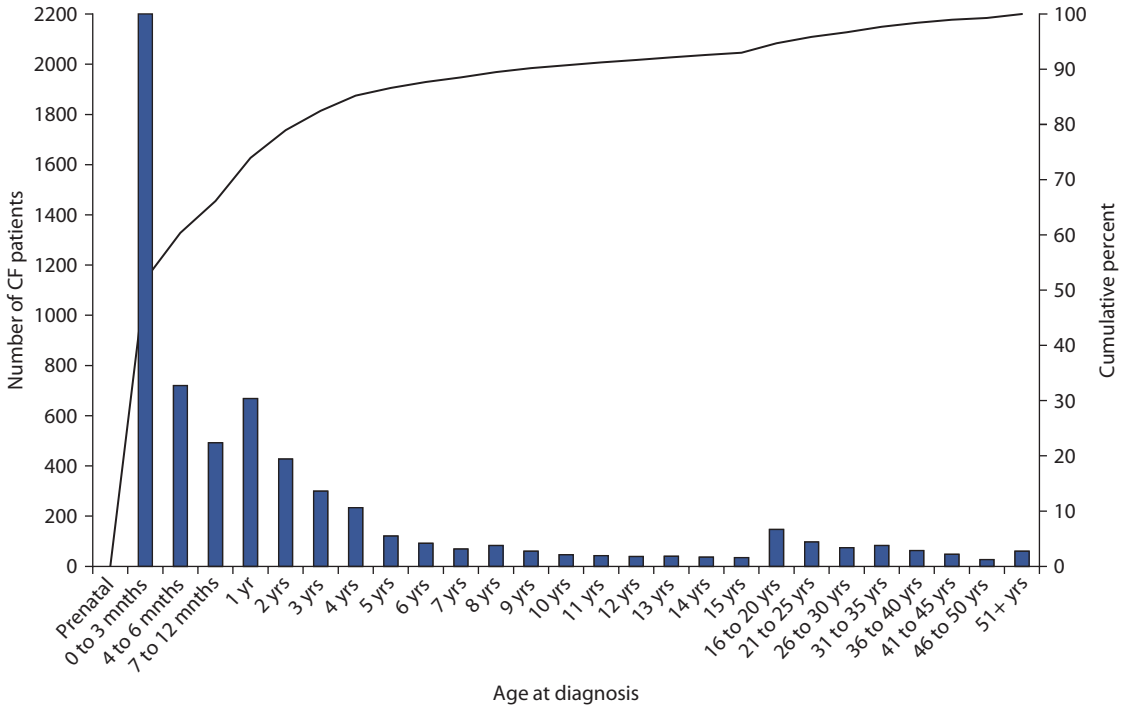

Figure 2.2 Distribution of age at diagnosis of patients seen in the United Kingdom in 2011 (including those diagnosed in 2011 and earlier). (From CF Trust, *Cystic Fibrosis Trust Annual Data Report 2011*, 2013.)

was 59%.[1] 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.[4] 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.[76,77] 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,[76,77] being more likely to be pancreatic sufficient.[76–79] Sweat chloride levels in these patients also tended to be lower[76,77] and, while the presence of an *F508del* genotype was common, patients diagnosed as adults were less likely to be homozygote *F508del*.[76–79] A number of the non-*F508del* mutations more common in patients diagnosed as adults were classes IV to V.[76,78]

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.[1] 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.

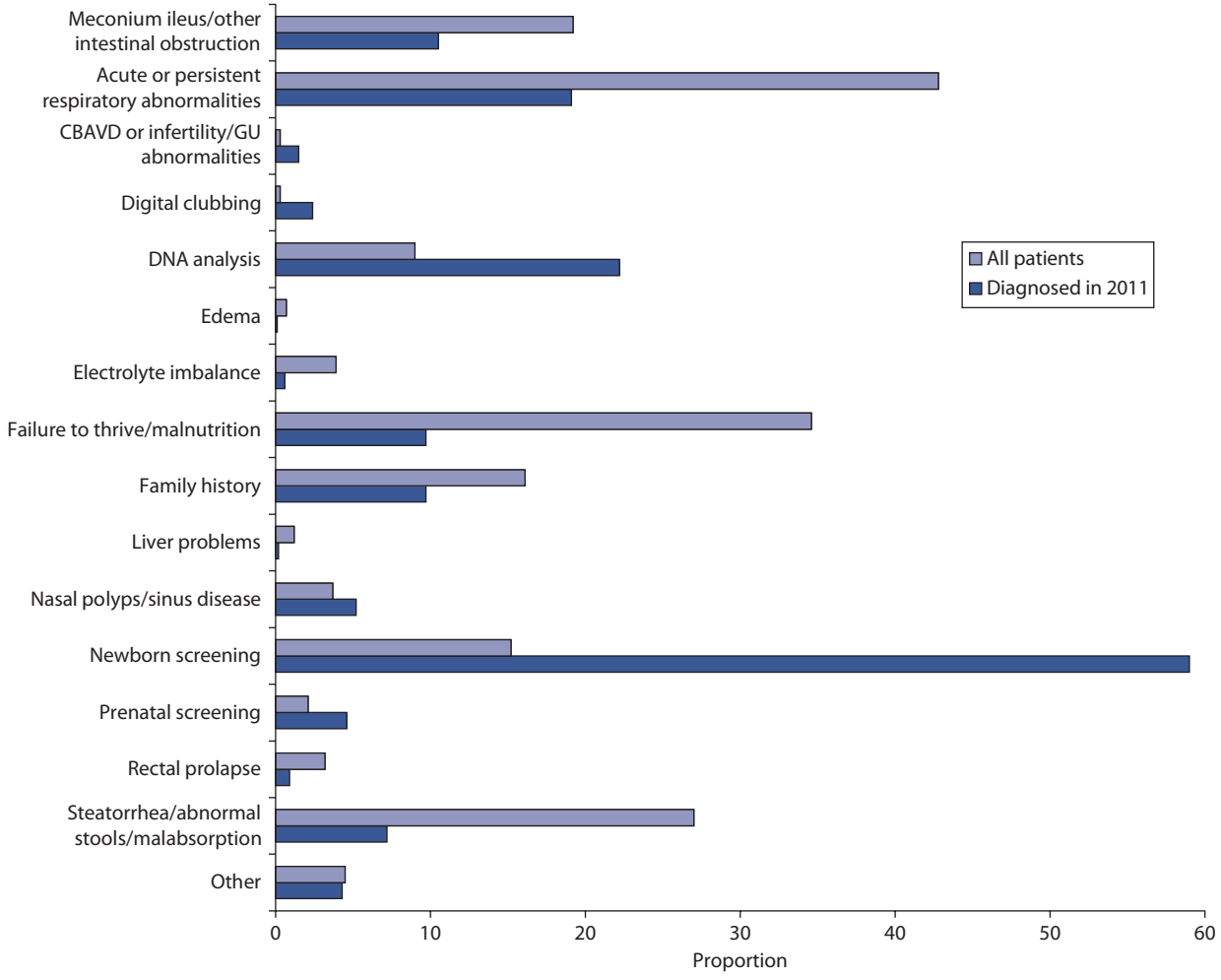

Figure 2.3 Clinical characteristics at diagnosis in all patients seen in 2011 and those diagnosed in 2011. Characteristics are not mutually exclusive and, as such, proportions do not add to 100. (From CF Foundation, Patient Registry 2011: Annual data report to the centre directors, 2012.)

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_1 (percentage predicted) was 74.7% for patients 6 years and older in the United Kingdom[2] and in the United States the mean was 77.1%.[1] 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[3] and 92.8% in Australia (2009).[5] For adults, these values were lower, 64.6% in Canada and 66.4% in Australia. This decline in FEV_1 with age was also seen in the United States[1] and is illustrated in Figure 2.4 using data from the UK registry. While this decline in FEV_1 with age is well documented, there is evidence to suggest that FEV_1 levels have improved over time. The US CFF presented a cross-sectional analysis of national data in 1991, 2001, and 2011 comparing median FEV_1 by age and found that while the decline with age was consistent in each period median FEV_1 values were higher in 2011 than in previous years. They also noted improvements in FEV_1 across successive birth cohorts.[1]

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.[80] used longitudinal data from the Danish CF registry where monthly measures of FEV_1 on all patients (1969–2010) showed that a change in FEV_1 % 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_1 % is a good predictor of future FEV_1 % 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_1, 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.[81] 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_1. 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.[82] observed that the rate of decline in FEV_1 in adolescence (14–17.4 years) is less than that in young adulthood (18.5–22 years).[82] Patients at a greater risk of decline include those who have had a slower rate of FEV_1 decline in adolescence, have greater FEV_1 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_1 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[1] (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

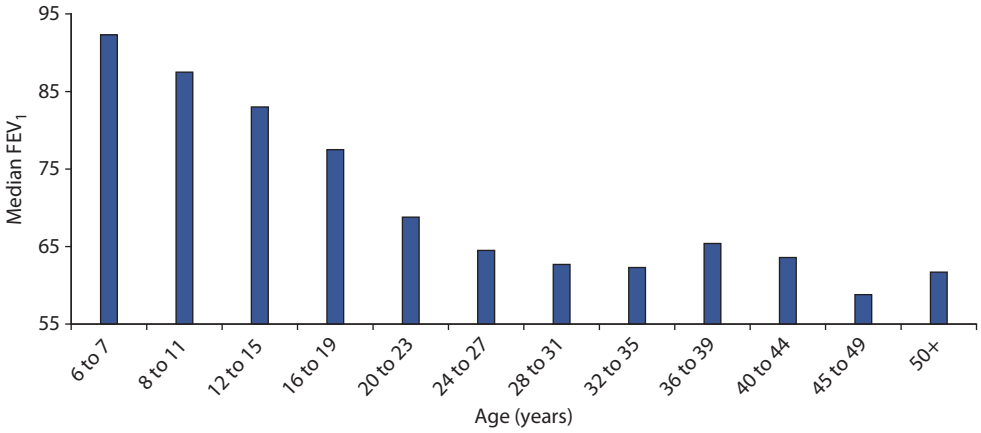

Figure 2.4 Median forced expiratory volume in 1 second percentage (FEV_1 %) predicted by age group. Note that the zero is suppressed. (From CF Trust, *Cystic Fibrosis Trust Annual Data Report 2011*, 2013.)

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.

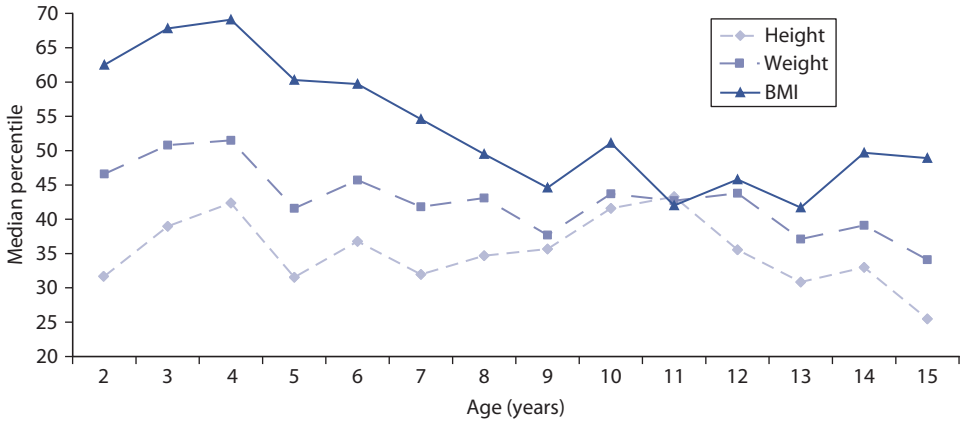

Figure 2.5 Median height, weight, and body mass index percentiles by age. (From CF Trust, *Cystic Fibrosis Trust Annual Data Report 2011*, 2013.)

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.[1,2] 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.[2] 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).[3] 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.[1]

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,[1] 22.1 in Canada,[3] 22.5 in Australia,[5] and 21.6 in the United Kingdom.[2]

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.[1–3,5] 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[1] compared with 2.6% in the United Kingdom,[2] 4.2% in Australia,[5] and 5% in Canada.[3] 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%.[1]

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.[83] It has been observed that in children *CFTR* genotype functionality is an important predictor of age of first acquisition of *P. aeruginosa*.[84] 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. aeurginosa*.[85] 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

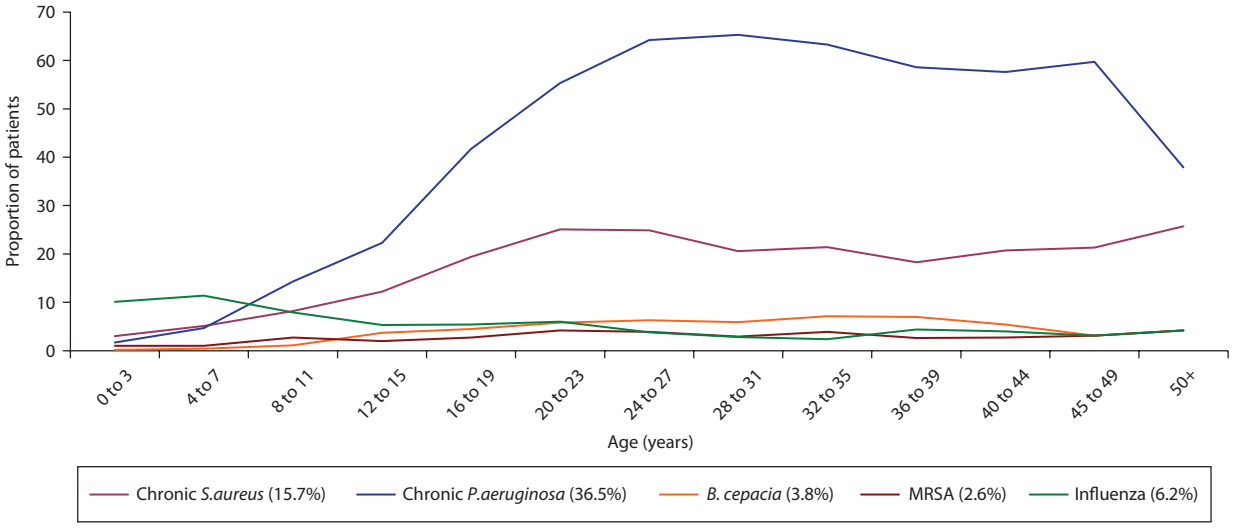

Figure 2.6 Age-specific prevalences of respiratory infections. (From CF Trust, *Cystic Fibrosis Trust Annual Data Report 2011*, 2013.)

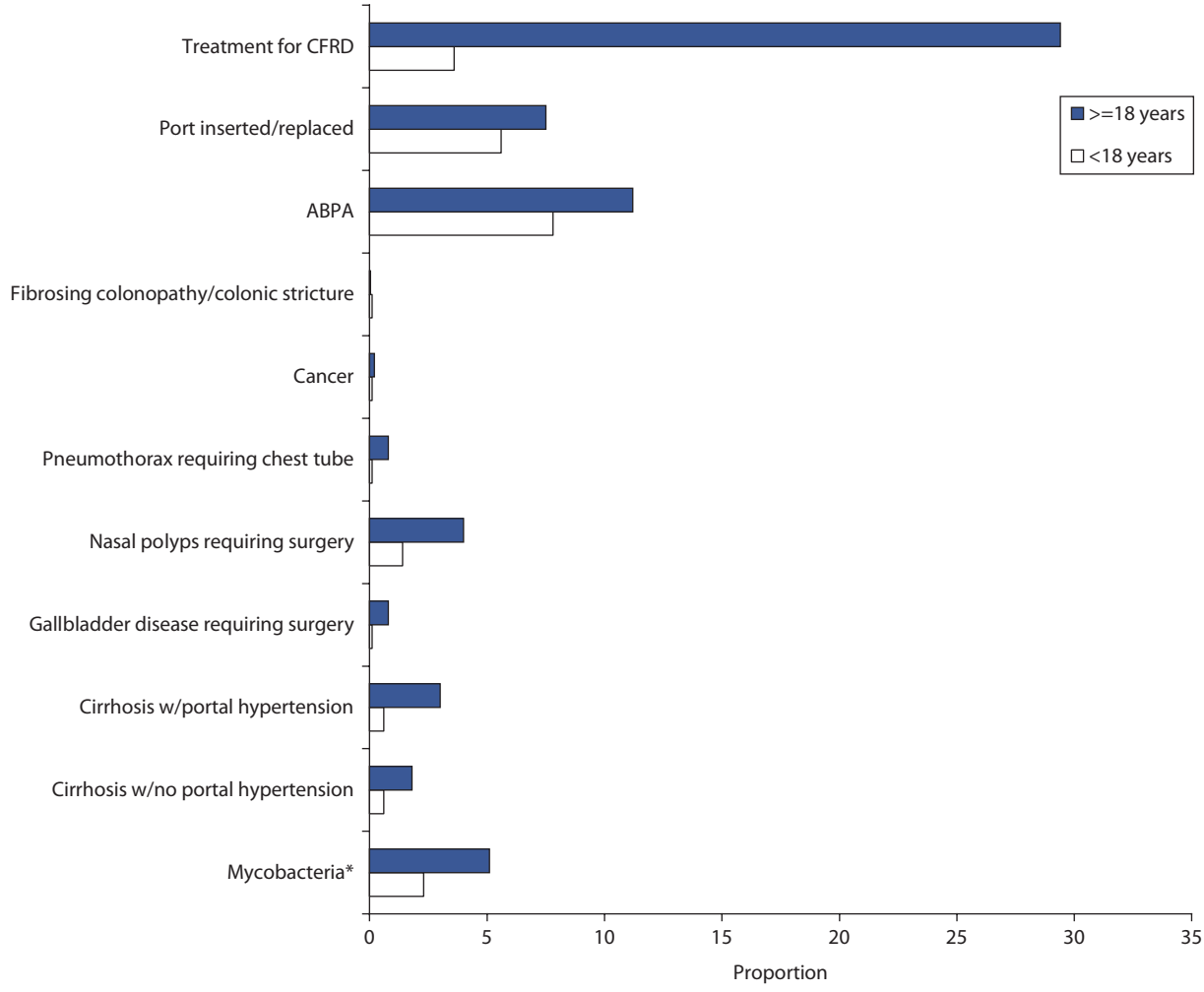

Figure 2.7 Proportion of patients with cystic fibrosis having different types of complications. The asterisk denotes nontuberculous or atypical. ABPA, allergic bronchopulmonary aspergillosis. (From CF Trust, *Cystic Fibrosis Trust Annual Data Report 2011*, 2013.)

these are CFRD and allergic bronchopulmonary aspergillosis[2] (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%).[1] 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[1] 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.[3]

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.,[86] 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.[1] In the United Kingdom in 1990, Walters et al.[86] 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.[87] A number of smaller surveys at single centers have shown that some patients felt that they had to leave their studies due to CF.[88,89] This is supported by Walter et al.'s[86] 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[86] 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[2] 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.[1] 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.[90] Other cross-sectional studies in the United States and elsewhere have noted varying levels of employment ranging from 48% to 72%.[88,91–93] 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_1 differed by whether patients worked and both groups had low lung function.[92] 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.[92] 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_1 and were less likely to have *P. aeruginosa*.[94] 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_1 and had spent less time in hospital.[95] As predictors of being in employment, however, the researchers showed that socioeconomic deprivation as measured at the postcode level modified the effect of FEV_1 such that FEV_1 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.[86] observed that adults with CF in work were more likely to be in nonmanual jobs compared to both the general population and their parents.[86] In a survey in the United States, 53.4% of adults in work were in professional,

technical, managerial, or professional roles.[92] In other US surveys, between 42% and 53% of adults were in professional or managerial roles.[87,96] 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."[88]

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,[91,96] although only a quarter had discussed their career choice with their doctor.[91] 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,[91] 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.[88] At least a quarter of respondents in two of these surveys reported having taken a salary cut due to their CF.[88,91] 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.[97,98] When incorporating data on functional class, however, researchers have found that those with a more severe genotype had worse survival. Lai et al.[99] 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.[57] 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.[56]

Pancreatic sufficiency

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

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.[64,101,102] 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.[64,97,99,100,103–105] 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.[106] Sex also features in a number of multivariate prognostic models,[107–109] although not all.[110–112]

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.[113] Assael[68] also found no evidence of a gender difference in a much smaller study in Verona as in other smaller studies elsewhere.[98,114]

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_1 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.[115] 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[101] 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.[64]

In the United States, Schechter et al.[116] 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_1 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.[117]

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.[99] 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[68] and in Israel Efrati et al. found that survival did not differ by whether or not the patient had meconium ileus.[118]

MODIFIABLE FACTORS

Pulmonary function

In follow-up studies where clinical data are available, FEV_1 % predicted at "baseline" (whenever this might be) has routinely been found to be positively associated with survival.[57,98,100,104,105,119] Kerem found that both FVC (forced vital capacity) and FEV_1 predicted survival.[103]

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_2 was predictive of survival rather than FEV_1[120]; yet another found that in a model containing both variables only FEV_1 was predictive.[121]

Nutrition

The importance of maintaining good nutritional health in CF patients has long been appreciated.[122] 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.[57,98,100,103–105,123,124] 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.[122] 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_1 was incorporated into the model.[119] Similarly, in a large national registry study in Canada researchers found that after adjusting for sex, FEV_1, and *B. cepacia* infection, infection with *P. aeruginosa* was no longer significantly associated with survival.[104] 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_1 and other characteristics.[57,100]

Patients with *B. cepacia* had worse survival than those without,[125] and patients are less likely to reach the age of 18 years.[99] Worse survival has been observed after adjusting for sex, FEV_1, and *P. aeruginosa*.[104,105] Chamnan[105] 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*.[126]

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

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.[105]

A smaller, earlier study in the United States suggested that the effect of CFRD on survival might be most evident in females[127] (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_1, and white blood cell count.[111] In the United States, Liou et al. developed a 5-year survivorship model using registry data, which included age, FEV_1, gender, weight for age, whether or not the patient was pancreatic sufficient, CFRD, *S. aureus* infection, *B. cepacia*, and the number of exacerbations.[107] Another model using US Registry data predicting 2-year mortality included age, height, FEV_1, hospitalizations, the number of home IVs, and respiratory infections (*B. cepacia* and *P. aeruginosa*).[112]

There is also some evidence that models developed in one setting many 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_1, *S. aureus* infection, *B. cepacia* infection, and the number of pulmonary exacerbations per year.[110] 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.[128] 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.[129] 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,[15] and a small study in Holland also noted an improvement in those receiving specialist care.[130]

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_1.[131] Mahadeva et al.[132] 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_1 occurred. Conversely, in Belgium researchers noted that patients who were referred earlier for specialist care had higher FEV_1 and less *P. aeruginosa*.[133]

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.[134] 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.[135] 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_1) 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.[136]

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").[137] The researchers did not observe any differences in nutritional outcomes or therapies used between the three models of care, but FEV_1 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_1, *P. aeruginosa*, or height/weight z-scores.[138] Similarly, in the Netherlands researchers noted no differences in annual changes in FEV_1, FVC, and BMI between pediatric patients receiving center, local, or shared care.[139]

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.[138]

SOCIOECONOMIC STATUS

As noted previously, a number of studies have observed that individuals from more socioeconomically deprived backgrounds have poorer survival[64,97,101,116] 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_1[116,140–143] and nutritional outcomes.[116,140,142,143] Quittner et al.[140] also noted that Medicaid patients reported poorer quality of life in analyses.

Interestingly, while FEV_1 was found to vary by neighborhood-level income in Canada[141]—a result also noted in the general population[144]—no association was observed between income and hospitalization for respiratory conditions after adjusting for FEV_1. The researchers postulated that this lack of association may reflect that most admissions were respiratory related. In the United States, however, Schechter et al.[116] noted that among children those on Medicaid were more likely to have hospitalizations and pulmonary exacerbations despite adjusting for FEV_1 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.[143] 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.[145]

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.[89] 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.[134]

Studies in the United States have shown somewhat mixed findings when considering the amount of contact with specialist services. Schechter et al.[116] did not observe a difference in the number of clinic visits by Medicaid status, whereas Nathanson et al.[146] 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.[147] 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.[147] 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."[148] 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,[149] a number of studies have been published in the last 5 years. Adopting a quality improvement approach has yielded improvements in BMI[150] and FEV_1[150,151] in pediatric clinics, identified potential failures in newborn screening before they occurred,[152] helped to develop a standardized strategy for evaluating the nutritional status of patients,[153] improved clinician adherence to prescription guidelines at a pediatric center,[154] and improved the success rate for sweat testing in infants.[155]

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."[156] A benchmarking

approach has also been recently launched in Germany using patient registry data.[157]

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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