

Evolution of Cystic Fibrosis Management in Ireland: A Comparative Three-Patient Case Series

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ABSTRACT

Cystic fibrosis (CF) management in Ireland has been limited to symptomatic and supportive treatment prior to the advent of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulator therapy. The implementation of national newborn screening in July 2011, and the development of highly effective modulator therapies have substantially altered the disease trajectory for many individuals with CF in Ireland. We describe three patients with CF treated at Cork University Hospital, each representing a distinct era of diagnosis and management. Patient 1, born in 1978, experienced the expected progression of CF in the pre-screening, pre-modulator era, culminating in bilateral lung transplantation at approximately age 22 and subsequent multisystem complications including chronic allograft rejection, chronic kidney disease (CKD) Stage 4, and Barrett's adenocarcinoma. Patient 2, born in 1988, was diagnosed in adolescence and experienced progressive lung disease prior to the availability of highly effective modulator therapy (HEMT); elexacaftor/tezacaftor/ivacaftor (ETI) improved FEV1 from 61% to 115%, however, established bronchiectasis remained irreversible. Patient 3, born in 2021, was diagnosed on day 3 of life via national newborn screening and commenced ETI granules at age two, with no evidence of chronic infection or structural lung damage to date. This case series illustrates how advances in newborn screening, CFTR modulator therapy, and centralised multidisciplinary care have fundamentally altered the trajectory of CF across successive generations of patients in Ireland. Early diagnosis and treatment may preserve near-normal organ function and life expectancy; however, inequities persist for patients ineligible for modulator therapy.

Categories: Pediatrics, Pulmonology, Internal Medicine

Keywords: Case series; cftr modulator; Cork university hospital; Cystic fibrosis; Elexacaftor/tezacaftor/ivacaftor; Highly effective modulator therapy; Ireland; Kaftrio; Lung transplantation; Newborn screening

INTRODUCTION

Cystic Fibrosis (CF) is an autosomal recessive disorder caused by pathogenic variants in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene, resulting in defective chloride ion transport, progressive obstructive lung disease, exocrine pancreatic insufficiency, and multisystem complications. Ireland has one of the highest global incidences of CF, at approximately 1 in 1,353 live births, with a gene frequency of approximately 2.6% and a notably high prevalence of specific variants including G551D.^[1,2] Prior to the development of targeted therapies, management was largely limited to symptomatic treatment, including physiotherapy, nutritional support, and antimicrobial therapy, and median survival rarely extended beyond the fourth decade.

Two developments have transformed the landscape of CF care and disease trajectory in Ireland. First, the introduction of national newborn screening in July 2011 facilitated earlier diagnosis and pre-symptomatic intervention, before irreversible organ damage is established.^[3] Second, the advent of CFTR modulator therapies, particularly elexacaftor/tezacaftor/ivacaftor (ETI), which goes by the trade name Kaftrio, has enabled direct correction of the underlying protein defect in eligible individuals. The pivotal phase 3 trial of ETI demonstrated a 14.3 percentage-point improvement in FEV1 and a 63% reduction in exacerbation rate,^[4] and subsequent modelling suggests that median predicted survival has increased from 38.6 to 68.0 years in the post-ETI era.^[5]

Ireland's centralised, nurse-led multidisciplinary CF care model is internationally recognised for its intensity and clinical outcomes. A time-driven activity-based costing study demonstrated that clinician time with patients was 108% greater in Ireland compared to a United States comparator site.^[6] Against this backdrop, this case series examines three patients born in 1978, 1988, and 2021, each representing a distinct era of CF diagnosis and management, to illustrate the cumulative clinical impact of these advances.

Methodology This is a retrospective, longitudinal, comparative case series of three de-identified patients from the adult and paediatric CF units at Cork University Hospital (CUH), selected to represent distinct eras of CF diagnosis and management in Ireland. Clinical data were extracted from de-identified medical records from each patient's clinical file at CUH, with written informed consent obtained from each patient and/or their parent or legal guardian. No interventions were performed for the purposes of this study. Patients are identified as Patient 1, Patient 2, and Patient 3, corresponding to birth years 1978, 1988, and 2021 respectively.

CASE PRESENTATION

Patient 1: Pre-Screening, Pre-Modulator Era (Born 1978)

Patient information and clinical findings. Patient 1 is an adult male with a genetically confirmed diagnosis of cystic fibrosis (homozygous F508del/F508del). He was diagnosed in childhood prior to the establishment of national newborn screening. His early disease course was characterised by progressive obstructive lung disease with chronic *Pseudomonas aeruginosa* colonisation, recurrent pulmonary exacerbations, and significant nutritional compromise secondary to exocrine pancreatic insufficiency.

Diagnostic assessment and therapeutic interventions. Management in the pre-modulator era consisted of intensive airway clearance physiotherapy, antimicrobial therapy during exacerbations, pancreatic enzyme replacement, and nutritional supplementation. Despite optimal supportive care, lung function declined progressively. Bilateral lung transplantation was performed at approximately age 22 for end-stage CF lung disease. He subsequently developed CKD necessitating a unilateral kidney transplant. CFTR modulator therapy is permanently contraindicated in this patient as the transplanted lungs do not carry the CFTR mutation.

Follow-up and outcomes. The post-transplant course has been complicated by chronic allograft rejection, CKD Stage 4 (eGFR approximately 26 mL/min/1.73m²), a STEMI, Barrett's adenocarcinoma, osteoporosis, and Bell's Palsy. He remains on life-long immunosuppression with tacrolimus, mycophenolate mofetil, and prednisolone, in addition to inhaled colomycin and tobramycin for chronic airway colonisation. His clinical course illustrates the irreversible multisystem morbidity that accumulated in the absence of early diagnosis and disease-modifying therapy.

Patient 2: Early Modulator Era (Born 1988)

Patient information and clinical findings. Patient 2 is an adult male with CF due to compound heterozygous F508del/G551D variants. He was diagnosed at approximately age 15 following a positive sweat test, during an era when newborn screening was not yet available. His early disease course was marked by progressive lung disease; chronic *Pseudomonas aeruginosa* colonisation was established from 2008, and cystic bronchiectasis was confirmed on computed tomography (CT) imaging in 2010. Peak lung function was recorded at 117.5% predicted forced expiratory volume in one second (FEV₁) in 2010, declining to 61% by 2020. Imaging from this pre-modulator period demonstrated the established cystic bronchiectasis (Figure 1).

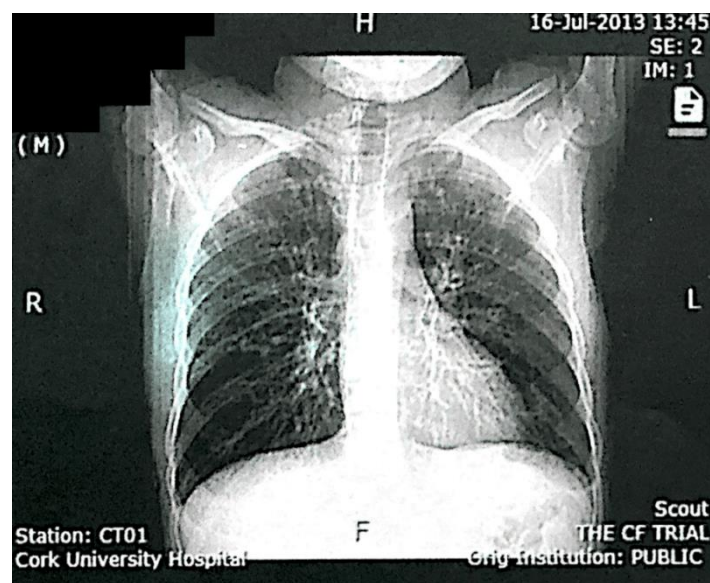


FIGURE 1: 2013 chest X-Ray showing bronchiectatic change involving all lung lobes, predominantly in the apices and apical lower lobes.

Diagnostic assessment and therapeutic interventions. He commenced ivacaftor monotherapy in 2020 following confirmation of the G551D gating mutation, with subsequent transition to ETI (elexacaftor/tezacaftor/ivacaftor; Kaftrio) in 2021. Within six weeks of ETI initiation, a clinically and statistically significant improvement in lung function was documented. FEV1 increased from 61% to 115% predicted by March 2023.^[4,7] Pulmonary exacerbation frequency decreased substantially, and nutritional status improved. Despite this marked functional recovery, imaging obtained during ETI therapy showed that the structural bronchiectasis persisted unchanged (Figure 2).

Follow-up and outcomes. Patient 2's current regimen includes Kaftrio, Kalydeco (ivacaftor), azithromycin (macrolide prophylaxis), omeprazole, pancreatic enzyme replacement (Creon), vitamin D3, Paravit CF, and montelukast. Despite the dramatic recovery in lung function, established cystic bronchiectasis has not reversed, illustrating the principle that highly effective modulator therapy (HEMT) can arrest progression but cannot restore pre-existing structural damage.^[4] Serial imaging on long-term ETI confirmed that the bronchiectasis remained structurally stable more than a decade after it was first documented (Figure 1). He is maintained on his current modulator regimen. His case demonstrates both the significant benefit and the inherent limitations of late modulator initiation.

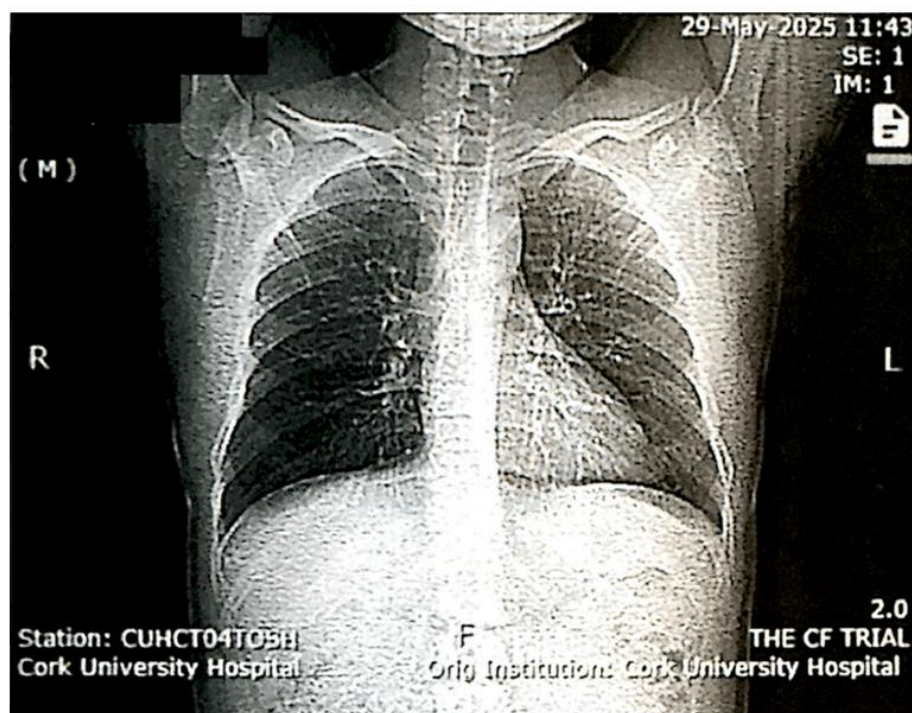


FIGURE 2: 2025 X-Ray showing stable bronchiectic change.

Patient 3: Newborn Screening and HEMT Era (Born 2021)

Patient information and clinical findings. Patient 3 is a female child with CF due to compound heterozygous F508del/Ile507del variants. She was diagnosed on day 3 of life via Ireland's national newborn screening

program. Her early clinical course included recurrent viral lower respiratory tract infections (LRTIs) in the first two years of life, consistent with normal infant susceptibility rather than CF-specific bacterial infection. A chest radiograph obtained during one such episode demonstrated right middle lobe consolidation with loss of the adjacent right heart border (**Figure 3**); follow-up imaging showed partial resolution, with the right heart border once again visible and only mild residual haziness remaining (**Figure 4**), consistent with a self-limiting infective process rather than established structural lung disease. Crucially, *Pseudomonas aeruginosa* has never been isolated from respiratory cultures, and no structural lung damage has been identified to date.

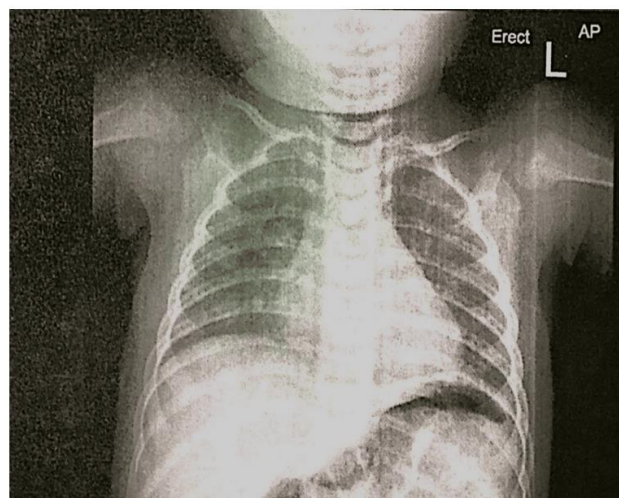


FIGURE 3: AP chest radiograph demonstrating right heart border silhouetting consistent with right middle lobe consolidation or atelectasis (compare with follow-up, **FIGURE 4**).

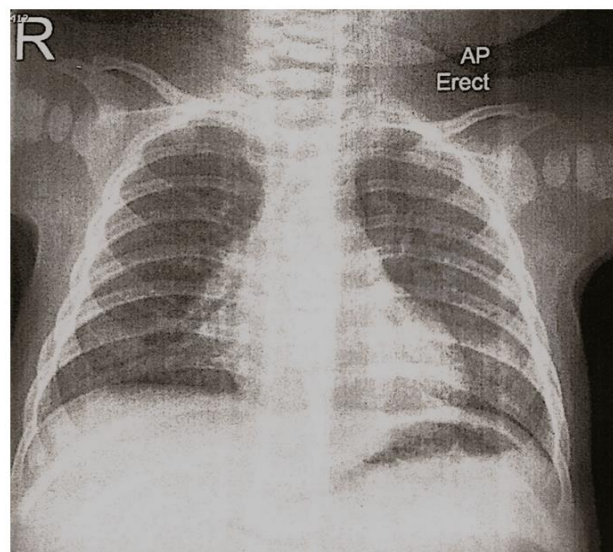


FIGURE 4: Follow-up chest radiograph demonstrating partial resolution of the right middle lobe consolidation seen previously (**FIGURE 3**), with the right heart border now visible but persistent mild residual haziness.

Diagnostic assessment and therapeutic interventions. She was commenced on Kaftrio granules (eleacaftor/tezacaftor/ivacaftor, paediatric formulation) at age two in 2024, in line with expanded licence criteria and CUH paediatric CF unit protocols.^[8] Pancreatic enzyme replacement with Creon, which had been initiated at diagnosis for exocrine pancreatic insufficiency, was subsequently discontinued following initiation of Kaftrio, reflecting restoration of some CFTR function.^[8] Current medications include Kaftrio granules, flucloxacillin (prophylactic), salbutamol as required, and saline nasal spray.

Follow-up and outcomes. Lung function testing is not yet applicable at preschool age. Patient 3 is developmentally appropriate and growing well. Transition to Alyftrek (deutivacaftor/tezacaftor/vanzacaftor) is planned at age 6 per current pathway guidance.^[9] Her clinical trajectory, including the absence of chronic bacterial infection and structural lung disease at the time of writing, represents a paradigm shift in what is now achievable with early diagnosis and pre-symptomatic HEMT initiation.^[3,10]

Patient Summary Table:

The following summary table (Table 1), displays a summary of the three patients and relevant information that has been compared between them in this case series.

	Patient 1	Patient 2	Patient 3
Year of Birth	1978	1988	2021
Genotype	F508del / F508del	F508del / G551D	F508del / Ile507del
CF Centre	CUH Adult CF Unit	CUH Adult CF Unit	CUH Paediatric CF Unit
Diagnosis	Childhood; pre-screening era	Age ~15; positive sweat test	Day 3 of life; national newborn screening
Peak FEV ₁	Pre-transplant	117.5% (2010)	N/A — preschool age
FEV ₁ at Lowest	End-stage; transplanted ~age 22	61% (2020)	N/A
FEV ₁ on HEMT	Ineligible	115% (March 2023)	N/A
Chronic Pseudomonas	Yes	Yes — from 2008	Never isolated
Structural Lung Damage	Severe — end-stage pre-transplant	Cystic bronchiectasis confirmed 2010	None to date
Pancreatic Insufficiency	Yes	Yes	Yes — Creon discontinued post-Kaftrio
Transplant	Bilateral lung transplant ~age 22	None	None
CFTR Modulator	Ineligible (post-transplant)	Ivacaftor 2020 → ETI (Kaftrio) 2021	Kaftrio granules from age 2 (2024)
Next Modulator Step	Ineligible	Current regimen maintained	Alyftrek at age 6
Key Complication(s)	Chronic transplant rejection, CKD Stage 4, STEMI, Barrett's adenocarcinoma, osteoporosis, Bell's Palsy	Established bronchiectasis despite lung function recovery on HEMT	Recurrent viral LRTI in first two years; no chronic bacterial infection
Current Medications	Tacrolimus, Mycophenolate, Prednisolone, Inhaled Colomycin, Inhaled Tobramycin	Kaftrio, Kalydeco, Azithromycin, Omeprazole, Creon, Vitamin D3, Paravit CF, Montelukast	Kaftrio granules, Flucloxacillin, Ventolin PRN, Sterimar

TABLE 1: Comparative clinical summary of three patients representing distinct eras of cystic fibrosis management in Ireland.

HEMT, highly effective modulator therapy; FEV₁, forced expiratory volume in one second; CKD, chronic kidney disease; ETI, eleacaftor/tezacaftor/ivacaftor; LRTI, lower respiratory tract infection.

DISCUSSION

This case series spans five decades of cystic fibrosis care in Ireland and captures the clinical consequence of each major therapeutic advance. The divergence in outcomes between the three patients is striking and is directly attributable to the era of diagnosis and the availability of disease-modifying therapy.

Patient 1's course represents the complete natural history of CF in the absence of either newborn screening or modulator therapy. Progressive lung disease, chronic bacterial colonisation, and multisystem complications led to bilateral lung transplantation at approximately age 22, a trajectory now increasingly rare in contemporary practice. The post-transplant complications he has experienced, including chronic allograft rejection, renal failure, malignancy, and cardiovascular disease, reflect the cumulative organ toxicity of long-term immunosuppression and underscore the irreversibility of disease that has run its premodulator course. His permanent ineligibility for CFTR modulator therapy represents an unresolved inequity in the current therapeutic landscape; approximately 6.7% of Irish people with CF remain ineligible for HEMT due to rare mutations or post-transplant status.^[11]

Patient 2 illustrates both the transformative potential and the inherent limitation of late modulator initiation. The improvement in FEV₁, from 61% to 115% following ETI is one of the most dramatic responses documented in the published literature and is consistent with the pivotal phase 3 trial findings.^[4,7] However, the cystic bronchiectasis established prior to ETI access has not resolved. Structural damage, once established, is irreversible.^[5] This is the critical lesson of the transition era: modulator therapy can arrest and partially reverse functional decline, but it cannot restore the architecture of damaged airways. Patient 2's case makes the strongest possible argument for pre-symptomatic diagnosis and treatment.

Patient 3 embodies the aspirational endpoint of contemporary CF care. Diagnosed on day 3 of life, before the onset of any symptomatic disease, and commenced on HEMT at age 2, she has no chronic infection and no structural lung damage. The discontinuation of pancreatic enzyme replacement following Kaftrio initiation, an outcome that would have been inconceivable a generation ago, reflects restoration of meaningful CFTR function.^[8] Real-world data from newborn screening cohorts support the hypothesis that early HEMT initiation is associated with sustained pulmonary preservation and deferred systemic complications.^[3,10]

Ireland's centralised, nurse-led CF care model has been an important structural contributor to these outcomes. The model provides intensive, coordinated multidisciplinary care that reduces fragmentation, supports adherence, and facilitates early intervention.^[6,12,13,14] Patient 3's family identified the CF multidisciplinary team as essential for reducing decision fatigue, financial strain, and care burden, factors that are increasingly recognised as determinants of treatment adherence and clinical outcome in chronic paediatric disease.

Several limitations of this case series merit acknowledgement. The descriptive, retrospective design limits statistical inference. Selection of three patients, while purposive, does not represent the full spectrum of CF phenotypes in Ireland. Patient 3's long-term outcomes remain unknown and will require extended follow-up to

confirm whether the preservation of lung architecture observed to date is sustained into adulthood. Additionally, Patient 1's pre-transplant lung function data are incompletely available from historical records. Notwithstanding these limitations, the series is internally consistent and the clinical contrasts are clearly and reproducibly documented.

CONCLUSIONS

This three-patient comparative case series illustrates five decades of evolution in cystic fibrosis care in Ireland. The disease trajectory is closely linked to the era of diagnosis. Newborn screening and highly effective CFTR modulator therapy have together transformed CF from a progressive, fatal childhood condition into a manageable chronic disease for the majority of affected individuals, with median predicted survival now approaching that of the general population in the post-ETI era.

However, significant inequities persist. Patients who have undergone lung transplantation, or who carry rare or non-responsive mutations, remain excluded from modulator therapy. Ensuring that these individuals are not left behind as the landscape of CF care continues to evolve remains an urgent clinical, ethical, and health policy priority.

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