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LETTER

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Benefits of reviewing pancreatic function in children with cystic fibrosis

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To the Editor,

Cystic fibrosis (CF) is a common autosomal recessive disease that causes pancreatic exocrine insufficiency (PI) in 90% of cases.[1] Over the last decade new CF transmembrane conductance regulator (CFTR) protein modulator therapies, like ivacaftor, have become available. Ivacaftor can cause children with a gating mutation, up to 14 years of age, born with a meconium ileus to become pancreatic exocrine sufficient (PS).[2] Of note, children with residual CFTR function mutations may be PI in infancy and then spontaneously become PS.[3]

Current recommendations from the Nutrition guidelines for CF in Australia and New Zealand suggest all children with CF have pancreatic function tested at diagnosis.[1] It is also suggested that repeat testing can help guide pancreatic enzymes replacement therapy (PERT) in patients on CF modulators. In the United States, guidelines for testing are recommended at diagnosis, with repeat testing to be considered in preschoolers or in patients with PS.[4–6] The aim of this study was to evaluate the benefit of reviewing pancreatic function testing and diagnosis of PS/PI of a cohort of CF patients and offering repeat testing to patients who had potential to become PS since initial testing.

Institutional ethics approval including waiver of informed consent was granted before commencement of the study. All children with CF living in Western Australia were included. Retrospective review of the following included age, sex, birthplace, genotype, and eligibility for and prescription of modulator therapy, current pancreatic function status, previous testing, meconium ileus at birth, and if prescribed PERT. After review, patients who had potential to become PS were offered testing prospectively.

There was 204 children and adolescents with CF being managed at Perth Children's Hospital the only tertiary pediatric hospital in Western Australia, at the end of 2019. Ninety-five (46%) were males, with an age range of 0–18 years. Exocrine pancreatic function had been tested in 177/204 (86%), with the majority having fecal pancreatic elastase testing. Out of the tested cohort 73% were diagnosed as PI (130/177).

IVACAFTOR

All 12 patients eligible for ivacaftor were pancreatic insufficient, 11 were on PERT (Table 1). One patient ceased ivacaftor due to poor tolerance. All taking ivacaftor were offered repeat testing. Eighty-one percent (9/11) completed this. Four had become PS since starting ivacaftor (one clinically), with three stopping PERT. Two of the three patients experienced recurrent abdominal pain when taking PERT, which resolved on ceasing. Time on ivacaftor to stopping PERT varied from 14 months to 3 years. Age at stopping was 5, 9, and 10 years. One infant who tested initially as PI was not started on PERT due to

TABLE 1 Pancreatic elastase at diagnosis and after starting ivacaftor

	Gene 1	Gene 2	Pancreatic elastase (normal > 200 μg/g)	Pancreatic elastase post starting ivacaftor	Currently taking PERT	Time on ivacaftor
1	p.[Phe508del]	p.[Gly551Asp]	<15	23	Yes	4 years
2	p.[Phe508del]	p.[Gly551Asp]	<15	24	Yes	3 years
3	p.[Ser549Asn]	p.[Lys684AsnfsX38]	58	410	No	Ceased PERT after 2.5 years on ivacaftor
4	p.[Phe508del]	p.[Gly551Asp]	<15	Nil	Yes	5 years
5	p.[Phe508del]	p.[Gly551Asp]	Nil	Nil	No	Ceased PERT after 14 months on ivacaftor
6	p.[Phe508del]	p.[Gly551Asp]	120	400	No	Ceased PERT after 3 years on ivacaftor
7	p.[Phe508del]	p.[Gly551Asp]	<15	23	Yes	3 years
8	p.[Gly551Asp]	p.[Glu193X]	<15	17	Yes	3 years
9	p.[Phe508del]	p.[Gly551Asp]	<15	15	Yes	5 years
10	p.[Phe508del]	p.[Gly551Asp]	<15	120	Yes	8 years
11	p.[Gly551Asp]	p.[Ser549Asn]	110	500	No	6 months
12	p.[Phe508del]	p.[Gly551Asp]	<15	Nil	Yes	0 years

Note: Patient 5 had never had pancreatic function tested and was clinically pancreatic sufficient after starting ivacaftor. Patient 11 was not started on pancreatic enzymes replacement therapy (PERT) and became pancreatic sufficient after starting ivacaftor.

lack of symptoms of malabsorption, became PS after 6 months of ivacaftor.

Other patients continue to be PI and on PERT despite being prescribed ivacaftor for up to 8 years. This includes an adolescent who developed pancreatitis twice after being on ivacaftor for 6 years. His pancreatic elastase has increased from <15 to 120 μg/g.

RESIDUAL CFTR FUNCTION

Of the 35 patients with at least one residual CFTR function mutation, 29 have had pancreatic elastase above 200 μg/g since diagnosis and one had never been tested however was clinically PS. Two had previously become PS before the age of 2 years. The remaining three were offered retesting. All completed with two becoming PS at age 3 and 16 years. See Table 2.

In this study there were three clear findings. First, treatment with ivacaftor is associated with a change from PI to PS in children with gating mutations. There are two multicentred studies that review pancreatic function in children with gating mutations on ivacaftor.[7,8] They include 12–24-month-olds and 2–5-year-olds. After 24 weeks of ivacaftor 18% –30% became PS. In our cohort 36% (4/11) became PS after starting ivacaftor. Children are more likely to change function if initial pancreatic elastase is more than 50 μg/g and if ivacaftor is started at a younger age. Potentially children eligible for ivacaftor at 1 year of age with borderline pancreatic function can now be managed without PERT if growing well. Of note, children 2–5 years with homozygous p.Phe508del have become PS on lumacaftor-ivacaftor in phase three studies to a lesser extent.[9,10] Also, elexacaftor–tezacaftor–ivacaftor may have more potential for change in pancreatic function, given it is a highly effective modulator like ivacaftor.

Second, children with PI and a residual CFTR function mutation can spontaneously become PS.[3] During this review, one patient with a residual CFTR function mutation continues to be PI. Most changed to PS before age 4 years and if their initial pancreatic elastase was over 150 μg/g.

Third, new abdominal pain or constipation when taking PERT may be a sign of change in pancreatic function in children with the potential to change. Fifty percent (2/4) of the children on ivacaftor experienced pain with PERT and one child with a residual CFTR function mutation became constipated before repeat testing. There are many causes of abdominal pain and constipation in CF, and change in pancreatic status should be considered. The limitations of this study are it is from a single centre. There are small numbers. Also, some results are limited by missing data especially in children who had moved to Western Australia.

The future of CF care is rapidly changing given the advancement of modulator therapy. Recurrent abdominal pain and constipation may be caused by improvement in pancreatic function. Regular reassessment of pancreatic function will prevent inappropriate PERT prescription and reduce side effects. Future research in this area should be included in multicentre phase 3 trials on new modulator treatment, especially if involving young children who are PI.

In children with CF, there is benefit to reviewing pancreatic function regularly. This review is especially important for patients on ivacaftor for a gating mutation or elexacaftor–tezacaftor–ivacaftor, have residual CFTR function mutations or have new abdominal pain when taking PERT.

TABLE 2 Pancreatic elastase at diagnosis and later, in children with a residual function mutation that initially were pancreatic insufficient

	Genotypes	Pancreatic elastase at diagnosis	Repeated pancreatic elastase
1	p.[Phe508del]/c.[2657+5G>A]	190	500
2	p.[Phe508del]/p.[Ala455Glu]	160	360
3	p.[Phe508del]/p.[Ille502Thr]	170	430
4	p.[Phe508del]/c.[2657+5G>A]	43	<15
5	p.[Phe508del]/[p. Arg1070Thr]		500

Note: Patient 5 was initially investigated with chymotrypsin, which was low.

AUTHOR CONTRIBUTIONS

Rachael Marpole: Conceptualization (equal), data curation (lead), formal analysis (lead), funding acquisition (lead), investigation (lead), methodology (lead), writing—original draft (lead), writing—review & editing (equal). **Andrew C. Wilson**: conceptualization (supporting); formal analysis (supporting); funding acquisition (supporting); investigation (supporting); methodology (supporting); writing—original draft (supporting); writing—review & editing (equal).

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author. The raw data are not publicly available due to ethical restrictions. Research data are not shared.

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