Real-World Assessment of Health Care Costs for Patients with Metastatic Pancreatic Cancer Following Initiation of First-Line Chemotherapy

Andrea Bullock, MD, MPH; Christopher G. Rowan, PhD;
Nina Oestreicher; Homa Yeganegi, MSc; and E. Gabriela Chiorean, MD

ABSTRACT

BACKGROUND: Management of metastatic pancreatic ductal adenocarcinoma (mPDA) places a significant financial burden on the U.S. health care system because of such factors as treatment with multidrug chemotherapy regimens, management of chemotherapy-related adverse events, and disease- or treatment-related hospitalizations. Depending on functional status, first-line chemotherapy regimens that are guideline recommended include *nab*-paclitaxel with gemcitabine (AG) and FOLFIRINOX (FFX), the combination of fluorouracil, leucovorin, irinotecan, and oxaliplatin. However, few previous studies have examined overall health care costs associated with mPDA management.

OBJECTIVE: To describe health care costs following initiation of first-line treatment with AG or FFX among patients with mPDA.

METHODS: Retrospective cohorts of first-line AG and FFX initiators were constructed from the MarketScan database (2014-2017). The index date was the date of first-line AG or FFX initiation. Included patients had insurance enrollment for 6 months before the index date. Total cumulative health care costs and costs from outpatient services, inpatient admissions, emergency department visits, chemotherapy administrations, and pharmacy dispensing were assessed within 12 months after the index date (i.e., 0-1, 0-2, ..., 0-12 months). Patient-level cost data began accruing from the first paid claim and continued accruing until the censoring date.

RESULTS: A total of 2,199 patients with mPDA initiated first-line AG (n = 1,352) or FFX (n = 847). Compared with AG initiators, FFX patients were younger (mean age 59 vs. 63 years) and had better baseline health status, with fewer having diabetes (43% vs. 57%) or coronary artery disease (12% vs. 22%). Median follow-up was 5.4 and 7.2 months for AG and FFX, respectively. Median first-line treatment duration was 2.1 months with AG and 2.3 months with FFX. Six months following first-line treatment initiation, total cumulative health care costs (median) were \$85,714 (95% CI = \$79,683-\$91,788) and \$114,116 (95% CI = \$105,816-\$119,591) for AG and FFX initiators, respectively. Outpatient services contributed the largest fractional cost for both groups.

CONCLUSIONS: Total health care costs for patients with mPDA who initiated FFX or AG are driven mostly by outpatient rather than inpatient costs. Further research, using comparative methodology, is warranted to fully understand cost drivers and whether higher costs for FFX patients relate primarily to use of FFX or higher underlying use of outpatient care among FFX patients.

J Manag Care Spec Pharm. 2020;26(7):872-78

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What is already known about this subject

- Metastatic pancreatic ductal adenocarcinoma (mPDA) is the most common type of pancreatic cancer and places a significant financial burden on the U.S. health care system.
- High costs associated with mPDA management have been attributed to treatment with multidrug chemotherapy regimens, management of treatment-related adverse events, and patient hospitalization.
- *Nab*-paclitaxel with gemcitabine (AG) and FOLFIRINOX (FFX) are first-line guideline-recommended chemotherapy regimens and are the 2 most commonly used regimens in the United States.

What this study adds

- This analysis showed higher first-line total health care costs associated with FFX than AG treatment, with the largest fractional costs attributed to outpatient services rather than inpatient admissions, although further study using methods controlling for selection bias are required to better understand cost drivers behind this result.
- The finding that AG initiators had higher chemotherapy drug costs, but lower overall health care costs, may be useful for treatment decision making by helping to inform how to appropriately allocate finite health care resources and forecast expenditures.

Metastatic pancreatic ductal adenocarcinoma (mPDA) is the most common type of pancreatic cancer and places a significant burden on the U.S. health care system. Despite accounting for only 3% of all new cancer cases (~50,000 new U.S. cases per year), mPDA is the third leading cause of cancer death in the United States.¹⁻³

Compared with other common cancer types, mPDA is associated with the highest monthly costs per patient.^{4,5} Costs associated with mPDA management have been attributed to chemotherapy drug costs and the costs to manage complications and side effects related to treatment where chemotherapy is the primary therapeutic option.^{1,5,6}

Depending on a patient's functional status and ability to tolerate antineoplastic therapy (i.e., kidney, liver, and bone marrow function), the National Comprehensive Cancer Network

guideline-recommended, and most commonly used, multidrug chemotherapeutic regimens for mPDA include nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) plus gemcitabine (AG) and fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX, abbreviated as FFX).⁷ The selection of AG versus FFX treatment usually depends on baseline patient characteristics, including patient performance status^{7,8}; nevertheless, even with significant differences in baseline patient characteristics, nearly equal use of AG and FFX was observed in 2 U.S. studies and a European study.⁹⁻¹¹ However, higher treatment-related costs (i.e., costs of drugs, administrations, supportive care, and managing adverse events) were associated with FFX use,¹¹⁻¹³ despite higher monthly drug-related costs for AG (\$12,221) compared with FFX (\$1,363).¹² While no randomized clinical trial has compared the efficacy of AG versus FFX, similar outcomes (i.e., median overall survival and progression-free survival) were observed with these regimens in retrospective observational studies.¹⁴⁻¹⁸

Few published studies have evaluated overall health care costs and cost drivers associated with the management of mPDA, beyond chemotherapy-related treatment costs or costs during first-line treatment. Given that health care systems have finite resources, there is increasing emphasis on the need for studies to evaluate overall health care costs, especially when considerable differences in treatment-related costs may exist and comparative effectiveness is uncertain. To provide a greater understanding of overall health care costs and cost drivers associated with the management of mPDA, this study aimed to describe health care costs for patients with mPDA who initiated AG or FFX as first-line chemotherapy regimens.

Methods

Study Design and Data Source

A retrospective cohort study of patients with mPDA who initiated AG or FFX as first-line chemotherapy regimen was conducted using the MarketScan Database (IBM, New York, NY). This U.S. data source includes employees and their dependents who are covered annually by a geographically diverse group of self-insured employers and private insurance plans. Patients with commercial and Medicare supplemental insurance were represented in the database, which links adjudicated medical, pharmacy, procedure, and diagnostic claims and associated costs for covered services in the inpatient and outpatient settings.¹⁹ All study data were accessed in compliance with U.S. patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996 regulations (HIPAA).

Study Cohorts and Inclusion/Exclusion Criteria

Among patients with mPDA whose first-line chemotherapy regimen was either AG or FFX, 2 mutually exclusive study cohorts were developed. Patients were eligible for inclusion

in the AG cohort if the first chemotherapy agent administered in the cohort identification period (January 1, 2014-June 30, 2016) was *nab*-paclitaxel or gemcitabine, with administration of the other agent within 15 days. Patients were eligible for inclusion in the FFX cohort if the first chemotherapy agent administered in the cohort identification period was fluorouracil (infusion or bolus), leucovorin, irinotecan, or oxaliplatin, with administrations of the other 3 agents within 15 days. The *nab*-paclitaxel and fluorouracil administration dates were assigned as the index date for each patient in the AG and FFX cohorts, respectively.

Patients were included in the AG and FFX cohorts if all of the following conditions were met: (a) aged ≥ 18 years at the index date; (b) ≥ 1 PDA diagnosis code within 6 months before or on the index date (*International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* [ICD-9/10-CM] codes: 157/C25); (c) ≥ 1 diagnosis code for a secondary malignancy (i.e., metastatic disease) before or within 45 days after the index date (ICD-9/10-CM codes: 196-197/C77-C79); (d) continuous insurance enrollment with medical and pharmacy benefits within 6 months before the index date; (e) no administration of chemotherapy agents, other than those included in the index regimens, within 6 months before the index date; and (f) no pancreatic neuroendocrine tumor diagnosis (ICD-9/10-CM codes: 157.4/C25.4) within 6 months before the index date.

Follow-Up and Censoring

Patients in both cohorts were followed from the index date to the first censoring event date. Censoring events included health plan disenrollment (≥ 45 -day gap in coverage), in-hospital death, the last available claim date for each patient (a proxy for death), or the end of available data (June 30, 2017).

Exposure Classification

An intention-to-treat approach was used to classify AG and FFX exposure during follow-up. With this approach, follow-up was not censored if the index chemotherapy regimen was discontinued, switched, or modified, and during analysis, patients remained in the group to which they were originally classified. No patient was assigned to both groups for the purposes of analysis.

Outcome Classification

Cumulative health care costs were determined from the payer-allowed cost (not including the patient contribution) from fully adjudicated, paid insurance claims in cumulative monthly intervals for 12 months following the index date (i.e., 0-1, 0-2, 0-3, ..., 0-12 months). The outcomes included the total cumulative median health care costs (payer allowed cost, U.S. dollars) and cumulative median costs stratified by costs for inpatient admissions, emergency department visits, outpatient service, chemotherapy drug administration, and

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pharmacy dispensing. Outpatient services costs included all costs from services incurred in the outpatient setting (e.g., drug administrations, infusion-related procedures, supportive care drugs, hydration, transfusions, ad hoc patient visits for palliative care, computerized tomography scans, and x-rays to assess complications). For each patient, cumulative health care costs began accruing on the date of the first paid claim after the index date (with a nonzero cost) and continued accruing until the censoring date. Patients were included in the cumulative monthly analyses from the month in which the first paid claim occurred through the month of the censoring date. Patients who did not incur costs in a particular stratum of interest (e.g., inpatient admissions) were not included in the cumulative cost analyses for that stratum but may have been included in other stratum specific cost analyses.

Statistical Analysis

For patients in the AG and FFX cohorts, baseline characteristics (collected within 6 months before the index date—including the index date) were summarized as means with standard deviations (SD) for continuous variables, and the number of patients and percentages for categorical variables. Median cumulative health care costs and 95% confidence intervals (CIs; calculated using the binomial method). All statistical analyses were conducted using Stata, version 15.1 (StataCorp, College Station, TX).

Results

Study Cohort Characteristics

A total of 2,199 patients met the study inclusion criteria, with 1,352 patients eligible for the AG cohort and 847 for the FFX cohort. Overall, 51% and 50% of patients eligible for the AG and FFX cohorts, respectively, were excluded from cohort entry. The criteria resulting in the greatest exclusion of patients were (a) not having evidence of metastatic disease (AG=27%, FFX=35%) and (b) not having 6 months of continuous insurance enrollment before the index date (AG=14%, FFX=13%).

Baseline Patient Characteristics

Baseline demographics, comorbidities, and health care resource utilization data are presented in Table 1. Compared with patients in the AG cohort, patients in the FFX cohort were younger and had fewer comorbid conditions (e.g., cerebrovascular disease, diabetes, chronic kidney disease, and congestive heart failure) and lower health care resource utilization.

Follow-Up, Duration of the Index Regimen, and Study Attrition

Patients in the AG and FFX cohorts were followed for a median of 162 days to the first censoring event for the AG cohort (mean [SD] 216 [94]) and 217 days for the FFX cohort (mean [SD] 260 [212]). The median duration of continuous exposure to the index regimen was 63 days for AG (mean [SD] 88 [93]) and

TABLE 1 Baseline Patient Characteristics

	AG	FFX
Patients, n	1,352	847
Demographics		
Age in years, mean (SD)	65 (9)	59 (8)
Aged <55 years, n (%)	164 (12)	235 (28)
Aged ≥75 years, n (%)	222 (16)	21 (2)
Female, n (%)	620 (46)	347 (41)
U.S. census region, n (%)		
Northeast	262 (19)	219 (26)
North Central	355 (26)	201 (24)
South	510 (38)	306 (36)
West	209 (15)	109 (13)
Unknown	16 (1)	12 (1)
Health insurance provider, n (%)		
Commercial	739 (55)	678 (80)
Medicare	613 (45)	169 (20)
Year of first PDA diagnosis, n (%)		
2013	88 (7)	48 (6)
2014	596 (44)	330 (39)
2015	378 (28)	243 (29)
2016	290 (21)	226 (27)
Comorbidities, n (%)		
Cerebrovascular disease	362 (27)	176 (21)
Chronic pulmonary disease	300 (22)	131 (15)
Diabetes mellitus	769 (57)	361 (43)
Chronic kidney disease	99 (7)	27 (3)
Congestive heart failure	161 (12)	62 (7)
Coronary artery disease	291 (22)	104 (12)
Cardiac dysrhythmias	345 (26)	173 (20)
Peripheral vascular disease	242 (18)	86 (10)
Acute myocardial infarction	54 (4)	15 (2)
Health resource utilization, n (%)		
Inpatient admission	918 (68)	508 (60)
Emergency department visit	625 (46)	388 (46)
Surgery	630 (47)	374 (44)
Radiation therapy	79 (6)	37 (4)

AG=nab-paclitaxel and gemcitabine; FFX=fluorouracil, leucovorin, irinotecan, and oxaliplatin; PDA=pancreatic ductal adenocarcinoma; SD=standard deviation.

70 days for FFX (mean 104 [108]). At 3, 6, 9, and 12 months following the index date, 80% versus 85%, 53% versus 64%, 34% versus 44%, and 21% versus 27% of patients for AG versus FFX cohorts, respectively, remained uncensored and were eligible for inclusion in the cumulative cost analyses. Censoring events were similar between cohorts—inpatient deaths were 15% and 16% for patients who initiated AG and FFX, respectively. However, shorter survival time was observed in patients who initiated AG; median survival was 107 days and 142 days for patients who initiated AG and FFX, respectively.

With the intention-to-treat approach, follow-up was not censored if the index chemotherapy regimen was discontinued or switched. Among patients who initiated AG, 30% later started treatment with a different chemotherapy agent (i.e., one not part

of the AG regimen). Among patients who started treatment with FFX, 48% later initiated a chemotherapy agent that was not part of the FFX regimen. Additionally, during follow-up, 95% of patients who initiated AG discontinued *nab*-paclitaxel, and 93% of patients who initiated FFX discontinued fluorouracil.

Outcome Results

Table 2 shows results for total cumulative health care costs and cumulative costs associated with inpatient admissions, outpatient services (including ambulatory care, procedures, medications, and diagnostic studies), emergency department visits, chemotherapy administrations, and pharmacy dispensing. Higher total cumulative health care costs were observed for patients with mPDA who initiated first-line FFX compared with first-line AG, with the cost differential increasing over time. Within 0-6 months after the index date, total cumulative health care costs (median) per patient were \$85,714 (95% CI=\$79,683-\$91,788) and \$114,116 (95% CI=\$105,816-\$119,591) for AG (n=719/1,352) and FFX (n=540/847) initiators, respectively. These numbers of patients represent 53% and 64% of the total AG and FFX samples, respectively. Within 0-12 months after the index date, total cumulative health care costs (median) were \$144,264 (95% CI=\$127,010-\$168,583) and \$203,224 (95% CI=\$186,701-\$217,481) for AG (n=282/1,352) and FFX (n=232/847) initiators, respectively. These numbers of patients represent 21% and 27% of the total AG and FFX samples, respectively. In order to be included in the 12-month cost analysis, patients had to have remained uncensored for at least 11 months and 1 day, resulting in lower total numbers of patients in the 0- to 12-month group than in the 0- to 6-month group.

Total health care costs were largely driven by outpatient costs for AG and FFX cohorts. For patients who initiated AG, outpatient costs were lower, while chemotherapy costs were higher compared with patients who initiated FFX. As evidenced by the overlapping CIs, no differences were observed for costs associated with inpatient admissions, emergency department visits, or pharmacy dispensing between cohorts.

Discussion

In this real-world study of health care costs associated with the management of mPDA, total (payer allowed) health care costs for patients with mPDA who initiated first-line therapy with FFX or AG were driven mostly by outpatient service costs (e.g., ambulatory care, procedures, medications, and diagnostic studies) rather than inpatient costs. We observed higher total costs of \$114,116 in the 6 months after the index date for patients who initiated first-line FFX, while total costs in the same time period for first-line AG initiators were \$85,714. The cost differential increased over time. Future studies could investigate the breakdown of outpatient costs and identify areas that principally contribute to outpatient health care costs.

Further investigation would also be required to understand whether the main drivers for higher cost among FFX patients are related to the use of FFX or to higher underlying use of outpatient care among FFX patients.

The findings of this study are consistent with previous research. In a health economic modeling study, Gharaibeh et al. (2017) projected greater economic benefit, in terms of cost-savings and cost-utility ratios, in favor of AG over FFX.¹³ In a retrospective study of claims data in the United States, McBride et al. (2017) found similar overall use of first-line therapy with AG and FFX, but AG was associated with lower costs from pharmacy dispensing, treatment administration-related procedures, and supportive care. However, they also found higher chemotherapy drug costs associated with AG use.¹¹

In contrast to studies reporting that hospitalizations accounted for the largest fraction of health care costs with nonmetastatic PDA,^{20,21} the results from the present study show that the largest cost driver for patients with mPDA was outpatient service costs. This finding is supported by the research of DaCosta Byfield et al. (2013) who found increased costs for mPDA compared with nonmetastatic disease were attributed to costs for chemotherapy drugs, targeted therapy, imaging, management of complications, and management of chemotherapy-related side effects.⁵ However, this may no longer be true given recent use of FFX for the management of nonmetastatic PDA.

The present study has several important strengths. This real-world, population-based study was broadly inclusive of patients with mPDA who initiated AG and FFX as the first-line regimen in the United States. The data source included complete ascertainment of health care costs from fully adjudicated, paid insurance claims for all covered services. In the absence of censoring follow-up at the time of discontinuing, modifying, or switching the index regimen, the results from this study depict overall health care costs throughout the patient journey of mPDA management. This approach contrasts with other studies that evaluated costs during first-line therapy only.

Limitations

This study does have some limitations to consider. One limitation relates to the unknown extent to which patients initiated a full or modified FFX regimen (e.g., the inclusion or omission of fluorouracil bolus, whether full doses or reduced doses of oxaliplatin or irinotecan were administered). Furthermore, performance status and survival data (apart from in-hospital discharge status and the last claim date that was used as a proxy for death) were not available from the insurance claims data. This is important, since mPDA patients with better performance status may be more likely to receive additional second- or third-line therapy and thus incur greater costs over time. In addition, the FFX cohort included a higher proportion of commercially insured patients (vs. Medicare enrollees),

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TABLE 2 Cumulative Median Health Care Resource Use Costs per Patient (USD): Total Costs and Costs by Service Type

	Months Post-Index Median Cost in USD (95% CI)			
	0-1	0-3	0-6	0-12
Total HRU costs				
AG	19,566 (18,586-20,553)	47,940 (45,563-50,387)	85,714 (79,683-91,788)	144,264 (127,010-168,583)
N (% of total AG initiators)	1,352 (100)	1,066 (79)	719 (53)	282 (21)
FFX	22,955 (21,347-24,469)	61,507 (57,834-66,342)	114,116 (105,816-119,591)	203,224 (186,701-217,481)
N (% of total FFX initiators)	847 (100)	717 (85)	540 (64)	232 (27)
Inpatient HRU costs				
AG	18,012 (16,068-19,690)	18,081 (15,717-22,006)	21,898 (18,793-24,824)	27,169 (23,999-34,199)
N (% of total AG initiators)	338 (25)	354 (26)	326 (24)	156 (12)
FFX	15,615 (13,903-20,099)	23,391 (19,592-26,502)	28,697 (24,874-33,586)	38,965 (30,283-42,822)
N (% of total FFX initiators)	191 (23)	246 (29)	216 (26)	117 (14)
Outpatient HRU costs				
AG	14,829 (14,275-15,408)	37,643 (36,238-39,349)	67,159 (63,503-71,247)	110,054 (102,482-123,277)
N (% of total AG initiators)	1,351 (100)	1,065 (79)	718 (53)	282 (21)
FFX	17,134 (15,812-18,523)	46,346 (42,623-49,047)	87,650 (81,089-95,641)	155,782 (141,887-169,918)
N (% of total FFX initiators)	847 (100)	717 (85)	540 (64)	232 (27)
Emergency department HRU costs				
AG	485 (413-569)	814 (725-996)	919 (755-1,094)	1,118 (927-1,488)
N (% of total AG initiators)	347 (26)	397 (29)	350 (26)	163 (12)
FFX	848 (684-1,000)	998 (805-1,229)	995 (851-1,245)	1,609 (1,091-1,965)
N (% of total FFX initiators)	201 (24)	270 (32)	239 (28)	117 (14)
Chemotherapy HRU costs				
AG	9,425 (9,003-9,905)	22,271 (21,123-23,738)	36,505 (34,409-38,220)	50,606 (45,819-57,050)
N (% of total AG initiators)	1,288 (95)	1,021 (76)	686 (51)	270 (20)
FFX	1,852 (1,571-2,113)	5,837 (4,879-6,688)	11,908 (9,550-14,127)	21,795 (16,654-26,704)
N (% of total FFX initiators)	806 (95)	686 (81)	517 (61)	222 (26)
Pharmacy-dispensing HRU costs				
AG	384 (325-429)	1,431 (1,255-1,589)	3,044 (2,627-3,464)	7,739 (6,748-8,891)
N (% of total AG initiators)	1,087 (80)	903 (67)	638 (47)	265 (20)
FFX	440 (365-537)	1,816 (1,502-2,107)	3,671 (3,067-4,146)	7,819 (6,157-9,789)
N (% of total FFX initiators)	680 (80)	596 (70)	467 (55)	204 (24)

Note: Total HRU payer-allowed costs are estimated for all patients who remained uncensored for at least 1 day within the last month of each time interval. Costs for each service type are estimated for all uncensored patients who incurred costs for that service type within each time interval.

AG = nab-paclitaxel and gemcitabine; FFX = fluorouracil, leucovorin, irinotecan, and oxaliplatin; HRU = health care resource utilization; USD = U.S. dollars.

compared with the AG cohort. Commercial payers often have higher payer allowed amounts than Medicare, which would tend to create higher costs for FFX versus AG patients.

This study was designed to report total health care costs for patients receiving first-line AG and FFX. It was not designed to make individual cost comparisons for AG and FFX cohorts. A

follow-up study, using comparative methodology (e.g., propensity score matching) to account for baseline performance status and comorbidities is needed.

Conclusions

In this population-based, real-world study of health care costs throughout the patient journey of mPDA management, costs from outpatient services made up the largest fraction of total costs for both AG and FFX cohorts. Further research, using comparative methodology to account for baseline performance status and comorbidities, is warranted to fully elucidate these findings and address the question of whether the potentially higher total costs of FFX patients are primarily caused by the use of FFX or by a higher propensity to use outpatient services among FFX patients.

Authors

ANDREA BULLOCK, MD, MPH, Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, Boston, Massachusetts.
CHRISTOPHER G. ROWAN, PhD, COHRDATA, San Clemente, California, and E. GABRIELA CHIOREAN, MD, Department of Medicine, University of Washington School of Medicine, Seattle, and Fred Hutchinson Cancer Research Center, Seattle, Washington.
NINA OESTREICHER, and HOMA YEGANEHI, MSc, Halozyme Therapeutics, San Diego, California.

AUTHOR CORRESPONDENCE: Andrea Bullock, MD, MPH, Beth Israel Deaconess Medical Center, Division of Hematology/Oncology, 330 Brookline Ave., Boston, MA 02215. Tel.: 617.667.2100; E-mail: abullock@bidmc.harvard.edu.

DISCLOSURES

This study was funded by Halozyme Therapeutics. Oestreicher and Yeganegi were employees of Halozyme Therapeutics at the time of the study and were involved in study design, data interpretation, and the decision to submit the data for publication. Bullock reports advisory board fees from Eisai, Exelixis, Bayer, and Taiho and consulting fees from Halozyme Therapeutics, outside the submitted work. Rowan reports consulting fees from Halozyme Therapeutics, during the conduct of the study. Chioresan reports grants and consulting fees from Celgene and Halozyme Therapeutics; grants from Lilly, Stemline, Ignyta, Roche, Merck, Boehringer-Ingelheim, Bristol Meyer Squibb, Incyte, MacroGenics, Rafael, and AADi; and consulting fees from Astra Zeneca, Array, Eisai, Ipsen, Five Prime Therapeutics, Seattle Genetics, Vicus, and Legend, outside the submitted work.

ACKNOWLEDGMENTS

Editorial support was provided by Rachel O'Meara, PhD, and Michelle Seddon, Dip Psych, both of Paragon, Knutsford, UK, supported by Halozyme Therapeutics.

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