Randomised clinical trial of an early palliative care intervention (SUPPORT) for patients with idiopathic pulmonary fibrosis (IPF) and their caregivers: protocol and key design considerations

Kathleen Oare Lindell,1 Mehdi Nouraie,2 Melinda J Klesen,1 Sara Klein,3 Kevin F Gibson,1 Daniel J Kass,1 Margaret Quinn Rosenzweig3

ABSTRACT

Introduction  Idiopathic pulmonary fibrosis (IPF), a progressive life-limiting lung disease affects approximately 128,000 newly diagnosed individuals in the USA annually. IPF, a disease of ageing associated with intense medical and financial burden, is expected to grow in incidence globally. Median survival from diagnosis is 3.8 years, and many of these patients succumb to a rapid death within 6 months. Despite the fatal prognosis, we have found that patients and caregivers often fail to understand the poor prognosis as the disease relentlessly progresses. Based on feedback from patients and families living with IPF, we developed the S-Symptom Management, U-Understanding the Disease, P-Pulmonary Rehabilitation, R-Palliative Care, O-Oxygen Therapy, R-Research Considerations and T-Transplantation (SUPPORT) intervention to increase knowledge of the disease, teach self-management strategies and facilitate preparedness with end of life (EOL) planning.

Methods  This study is a randomised trial to test the efficacy of SUPPORT intervention compared with routine care in patients with IPF and their caregivers delivered after three clinical visits. We are recruiting a cohort of 64 new IPF patient/caregiver dyads (32 for each dyad).

Results  The trial will evaluate whether the SUPPORT intervention decreases stress, improves symptom burden, quality of life, preparedness and advance care planning for patients and caregivers, quality of dying and death for caregivers if the patient dies during the course of the study, as well as assess the impact of primary palliative care on healthcare resource use near the EOL.

Conclusion  By increasing knowledge of the disease, teaching self-management strategies and facilitating preparedness with EOL planning, we will address a critical gap in the care of patients with IPF.

Trial registration number  NCT02929017; Pre-results.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive life-limiting lung disease that affects approximately 128,000 newly diagnosed individuals in the USA annually. IPF, a disease of ageing associated with intense medical and financial burden, is expected to grow in incidence within the US population and worldwide. Median survival from diagnosis is 3.8 years, and many of these patients succumb to a rapid death within 6 months. Despite the fatal prognosis, we have found that patients and caregivers often fail to understand the poor prognosis as the disease relentlessly progresses. New therapies have recently become available. These medications, however, slow the rate of deterioration of lung function but have no impact on ultimate survival or quality of life (QOL). Although transplantation is an effective surgical therapy, <20% of patients ever receive a lung transplant. The remaining 80% have few treatment options and are predicted to experience a rapidly progressive downhill course. Despite the fatal prognosis, we have found that patients and caregivers (CGs) often fail to understand the poor prognosis as the disease relentlessly progresses. At the end of life (EOL), patients with IPF and their caregivers experience stress, symptom burden, poor QOL and inadequate preparedness for EOL care planning.

Despite an extensive body of literature that supports palliative care (PC) as the quality standard of care in patients with life-limiting conditions, a major gap in the literature and practice reveals that referral to PC for patients with advanced lung disease commonly occurs late or not at all. We have identified reluctance to engage in advanced care planning on the part of patients and
caregivers with IPF.\textsuperscript{12-16} Based on the existing literature and our observations, we hypothesised that stress, symptom burden, poor QOL and poor care planning in patients with IPF and their caregivers can be overcome by early introduction of PC during IPF.\textsuperscript{17-20} Based on feedback from patients and families living with IPF, we developed the S-Symptom Management, U-Understanding the Disease, P-Pulmonary Rehabilitation, P-Palliative Care, O-Oxygen Therapy, R-Research Considerations and T-Transplantation (‘SUPPORT’) intervention to increase knowledge of the disease, teach self-management strategies and facilitate preparedness with EOL planning. The community of interest felt the term ‘SUPPORT’\textsuperscript{21} was associated with better understanding and more favourable impressions than ‘PC’.\textsuperscript{22}

The purpose of this study is to describe the early feasibility and acceptability of the SUPPORT intervention in patients with IPF and their caregivers. By increasing knowledge of the disease, teaching self-management strategies and facilitating preparedness with EOL planning, we will begin to address a critical gap in the care of patients with IPF and all patients with advanced lung disease (high medical utilisation and high symptom burden in the face of a fatal illness).

METHODS
Study design and setting
This study is a randomised trial to test the efficacy of SUPPORT intervention compared with routine care in patients with IPF and their caregivers. The University of Pittsburgh Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease (ILD) at UPMC, setting for this study, was established as a multidisciplinary centre devoted to research and treatment of ILD with a focus on IPF in 2001. The centre evaluates over 15–20 new patients with ILD monthly; of those 6–10 have a newly confirmed diagnosis of IPF. The centre has seen >5000 patients with ILD (>1000 with IPF).

**SUPPORT intervention**

The MacMillan Good Death Model (adapted)\textsuperscript{23,24} serves as the basis for the SUPPORT intervention pilot work and into the future. According to this model, stress, symptom burden, QOL and preparedness with advanced care planning (dependent variables) may be amenable to an early integrative PC intervention (independent variable). Stress is the primary outcome for the patient and caregiver, and the secondary outcomes include decreased symptom burden, increased QOL, increased preparedness and advance care planning for the patient. The secondary outcomes for the caregiver include increased preparedness, advance care planning and quality of dying and death (QODD) if the patient dies during the study. The intervention supports patients with IPF and their caregivers, and ultimately affects outcomes of the care including location of death, early PC referral and decreased deaths in intensive care unit. Here, the patient’s decision-making will drive the outcomes and enhance the QODD\textsuperscript{25} as experienced by the caregiver. The important factor influencing change is the (modifiable variable) degree to which there is knowledge regarding the disease, symptom management, treatment strategies and advanced care planning by the patient and their caregiver. According to the MacMillan Model, psychological symptoms (symptom burden and stress, and QOL, preparedness with advanced care planning) are modifiable and can be changed by a PC intervention (see table 1).

This intervention was developed in an iterative manner based on previous clinical experience,\textsuperscript{9,15,21} the literature endorsing the introduction of PC at the onset of serious illness\textsuperscript{26} and a community of interest. The primary

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Supportive care intervention component delivery schedule</th>
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</thead>
<tbody>
<tr>
<td>Intervention component</td>
<td>Rationale</td>
</tr>
<tr>
<td>1. Education: disease, typical disease course, prognosis, treatment options, including mechanical ventilation, intensive care unit (ICU) admission</td>
<td>Rare disease, patients/caregivers are often uninformed about disease course and prognosis and therefore unaware of likelihood of ICU hospitalisation</td>
</tr>
<tr>
<td>2. Self-management training for most common and distressing symptoms</td>
<td>Progression escalation of incapacitating symptoms, for example, cough, dyspnoea, hypoxaemia, role of pulmonary rehabilitation and oxygen therapy</td>
</tr>
<tr>
<td>3. Caring for caregiver</td>
<td>Impacts family due to rapid change in life status for previously healthy individual—CG often neglects own health</td>
</tr>
<tr>
<td>4. Planning for future and development of shared end of life (EOL) goals</td>
<td>Rapid progression of disease and lack of discussion prior often leaves CG without adequate preparation for making advance care planning and EOL decisions</td>
</tr>
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</table>
investigator conducted focus groups with patients with IPF and family caregivers to guide design of the proposed SUPPORT intervention. Focus group input identified that patients and caregivers experience limitations in the education received, overwhelming symptom burden and confusion with hospice and reluctance to engage in advanced care planning. The SUPPORT intervention was then further developed with input from ILD nurses, ILD physicians and preliminary testing on two patients with IPF and a health education curriculum advisor helped with finalisation of the intervention. The intervention is available in a book format, also on a university website with audio input, and delivered face to face by a nurse interventionist. This intervention is registered through the University of Pittsburgh Innovation Institute. Each component of this intervention provides health information that will allow the patient and their caregiver to be better informed about IPF. The goal is to provide information that better prepares patients for what to expect as the disease progresses and options that are available.

SUPPORT training
The nurse interventionist and research coordinator have received instructions in empathic communication, SUPPORT content and were trained in delivery of the intervention by the primary investigator. After completing training, the interventionist and research coordinator engaged in three separate simulated sessions with the PI to gain competency in delivery of the intervention. Using a manual for guidance, the SUPPORT intervention is delivered by the nurse interventionist who discusses each component of the intervention. Discussion is tailored according to questionnaire responses, emphasising areas of apparent knowledge deficit. To standardise content received, the interventionist will respond to questions by referencing the materials provided. If questions go beyond this content, the interventionist will counsel patients to consult their doctor and help the patient craft questions that address additional concerns. Weekly feedback sessions with the nurse interventionist and biannual group booster trainings are designed for skills maintenance and support. Intervention fidelity will be monitored via audiotape analysis. Every visit will be audiotaped and a randomly selected 20% reviewed by principle investigator (PI) (KOL) and mentor (MQR) for fidelity and quality. If protocol adherence drops below 80%, the PI (KOL) and mentor (MQR) will develop a remediation plan.

Sample selection and sample size calculation
Sample size calculation was based on previous work using the Perceived Stress Scale (PSS). On the other hand we expect no changes in the PSS in the control arm. A sample size of 32 in each arm will provide 90% power (α=0.05, two-sided test) to detect this difference. Therefore, we are recruiting a cohort of 64 new IPF patient/caregiver dyads. Considering a 20% drop out, the number of dyads that need to be approached to achieve the final desired sample size is 80. Previous research indicates a minimum 75% recruitment rate of eligible patients and caregivers. Conservatively, we expect accrual of four to six new patients each month.

The inclusion criteria for patients is: a diagnosis of IPF based on ATS criteria and the ability to read or speak English (questionnaires in English). The inclusion criteria for caregivers is: age ≥18 years, non-paid (eliminates professional caregivers), identified by patient as providing the majority of emotional, financial and physical support (individual most involved in care) and the ability to read and speak English (questionnaires in English).

Protocol
The clinician invites the dyad to participate in the study. If the dyad is agreeable, the research coordinator obtains informed consent. The SUPPORT nurse interventionist meets with the dyads in a private conference room, away from the clinic centre. Each dyad is given a questionnaire booklet with the three questionnaires (described below) with a total of 88 items to be completed by the patient and 16 items by the caregiver. Completion is expected to take in 30–45 min for the patient and 10–15 min for the caregiver. Due to the sensitive nature of the questionnaires, the patient and caregiver ideally complete questionnaires separately (table 2).

The scheduled clinic day is used as the randomisation unit to decrease the chance of contamination effect (communication between intervention and control group about interventional material). Dyads are randomised into the intervention or control group based on clinic day. Patients tend to return to clinic on the same day of the week as the original visit (eg, Thursday patients remain as Thursday patients even in follow-up). Clinical staff and physicians are blinded to the randomisation.

Intervention group dyads receive educational materials that are routinely distributed—the SUPPORT Intervention book, the link to a digital website with audio that complements the SUPPORT intervention book, and the intervention is delivered face to face by the nurse interventionist.

Usual care control
Control group dyads receive educational materials that are routinely distributed as usual care. All follow-up care and other aspects of care will proceed as per usual. At the completion of the study, usual care dyads will receive the SUPPORT intervention book, the link to a digital website with audio that complements the SUPPORT intervention book and the intervention is delivered face to face by the nurse interventionist.

Based on clinical experience, we elected to provide a hard copy of intervention content and a digital website with audio to accommodate different learning styles.
## Table 2  Study format and schedule: intervention and control group

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 (next visit after diagnosis confirmation)</td>
<td>Steps:&lt;br&gt;► Clinic visit—first visit after confirmation of diagnosis of IPF by patient’s clinician. &lt;br&gt;► Invitation to participate by clinician. If agreeable, RC will obtain informed consent, and provide with questionnaires and preparedness survey. &lt;br&gt;► If randomised to control group, RC will provide with routine printed patient education.&lt;br&gt;► If randomised to intervention group, RC will provide with routine printed patient education and introduce SUPPORT nurse interventionist. &lt;br&gt;► Interventionist will provide and review SUPPORT Intervention materials (see table 1). &lt;br&gt;► Interventionist will instruct SUPPORT intervention dyads in maintaining log of home use of SUPPORT materials (online supplementary appendix 1). &lt;br&gt;► First SUPPORT intervention session should take 60 min&lt;br&gt;► All control group and SUPPORT intervention patients will have scheduled next clinic visit in 3 months, provide number to call if questions.</td>
</tr>
<tr>
<td>Visit 2 3 months after visit 1</td>
<td>Steps:&lt;br&gt;► All SUPPORT intervention and control group dyads will have clinic visit with patient’s clinician. &lt;br&gt;► SUPPORT intervention group will have research visit with interventionist for delivery of intervention for approximately 60 min.</td>
</tr>
<tr>
<td>Previsit 3  Visit 3 3 months after visit 2</td>
<td>PI will speak with clinician to remind about addressing advanced planning prior to visit 3. Steps:&lt;br&gt;► All SUPPORT intervention and control group dyads will have clinic visit with patient’s clinician. All SUPPORT intervention dyads will have research visit with interventionist for delivery of intervention. This session should take approximately 60 min. &lt;br&gt;► All SUPPORT intervention and control group dyads will repeat questionnaires, knowledge survey, preparedness survey and evaluation.</td>
</tr>
<tr>
<td>Follow-up: at study close</td>
<td>All SUPPORT intervention and control group patients—patient care trajectory (ED visits, hospitalisations, formal palliative care referrals, location of death)</td>
</tr>
<tr>
<td>Caregiver Follow-up At study close</td>
<td>All SUPPORT intervention and control group caregivers—caregivers of patients who die during the study will be asked to contact the interventionist to provide this information and asked to complete the QODD instrument.</td>
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</table>

DLCO, diffusion capacity of the lungs for carbon monoxide; ED, emergency department; IPF, idiopathic pulmonary fibrosis; QODD, quality of dying and death; RC, research coordinator; SUPPORT, S-Symptom Management, U-Understanding the Disease, P-Pulmonary Rehabilitation, P- Palliative Care, O-Oxygen Therapy, R-Research Considerations and T-Transplantation.

preferences. Dyads are encouraged to review these materials at home and keep a simple self-report of when, what and how (format) reviewed. They are invited to call the interventionist with any questions and the interventionist will maintain a log of those calls.

### Data collection

**Intervention feasibility**: we record the numbers of dyads who are (1) eligible (2) consented, (3) enrolled and (4) completed the study. We record the time required for the questionnaire completion for the entire group and time for intervention in the SUPPORT intervention group. We describe reasons for refusal or attrition.

**Intervention acceptability**: following completion of the SUPPORT intervention, using a survey with five quantitative questions, patients and caregivers are asked to assess the acceptability of the SUPPORT intervention. They are asked about their satisfaction with intervention, materials, appropriateness of the intervention and if they found the individual instruction with the nurse helpful.

### Instruments

- **Demographics**: demographic variables collected will include age, gender, race and level of education (see table 3).
  - Disease severity data collected will include date of diagnosis, date of first centre visit, forced vital capacity% predicted, DLCO% predicted, oxygen test results and oxygen prescription.
- **Comorbidities**: recorded and patients are stratified based on number of major comorbidities (cancer, depression, hypertension, myocardial infarction, chronic heart failure, cerebrovascular accidents, diabetes mellitus, chronic kidney disease, chronic liver disease, cognitive impairment) in three groups. The effect of intervention is adjusted for comorbidities. We will use an existing comorbidity summary score, for example, Charlson Severity Index to assess the effect of comorbidities. Alternatively, we will create a study-specific comorbidity summary index using data dimension reduction for statistical analysis.
- **Knowledge survey**: this prepost survey measures the knowledge acquired from participating in this sup-
A supportive care intervention by asking 14 questions about content. This survey includes questions about each of the SUPPORT components.

- **Symptom Burden**: Patient Reported Outcome Measurement Information System (PROMIS-29); developed by the National Institutes of Health (NIH) to measure patient-reported outcomes is used to measure physical function, anxiety, depression, fatigue, sleep quality, satisfaction with social role and pain.28

- **A Tool to Assess QOL in IPF (ATAQ-IPF)**: specific symptom burden and health-related QOL is measured by the ATAQ-IPF, designed to include dyspnoea, cough, fatigue and general QOL in patients with IPF. It is composed of 43 items and 10 domains. Internal consistency and validity have been well established in patients with IPF.29 This instrument is the only QOL instrument specific to patients with IPF, and is under review by the Food and Drug Administration. At present, psychometric testing results are unavailable.

- **PSS**: the PSS is designed to measure the perceived stress of a situation and the degree to which subjects find their lives unpredictable, uncontrollable and overloaded. The range of scores is 0–40, with higher scores indicating more appraised stress. Internal consistency and validity have been well established in diverse populations.30

### Table 3 Variables for aims 1, 2 and 3

<table>
<thead>
<tr>
<th>Measure</th>
<th>Data source</th>
<th>Instrument timing</th>
<th>Measurement psychometrics (# items)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aim 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>Age, gender, race and education</td>
<td>Patient and caregiver</td>
<td>Visit 1</td>
</tr>
<tr>
<td>Disease severity</td>
<td>Forced vital capacity%, DLCO%, Oxygen yes/no, Date of diagnosis, Date of initial centre visit</td>
<td>Patient</td>
<td>Visit 1</td>
</tr>
<tr>
<td>Comorbidities</td>
<td># comorbidities</td>
<td>Patient</td>
<td>Visit 1</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Time, attendance</td>
<td>Patient and caregiver</td>
<td>All visits and study close</td>
</tr>
<tr>
<td><strong>Aim 2 mediating variable</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Knowledge</td>
<td></td>
<td>Patient and caregiver</td>
<td>Visit 1 and 3</td>
</tr>
<tr>
<td>Acceptability of intervention</td>
<td>Survey</td>
<td>Patient and caregiver</td>
<td>Study close</td>
</tr>
<tr>
<td><strong>Aim 3 outcomes of intervention and evaluation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td>Stress</td>
<td>Patient and caregiver</td>
<td>PSS</td>
</tr>
<tr>
<td>Symptom burden</td>
<td>Physical function, anxiety, depression, fatigue, sleep quality, satisfaction with social role and pain</td>
<td>Patient</td>
<td>Patient Reported Outcome Measurement Information System-29</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Quality of life</td>
<td>Patient</td>
<td>A Tool to Assess QOL in IPF</td>
</tr>
<tr>
<td>Disease preparedness</td>
<td>Survey</td>
<td>Patient and caregiver</td>
<td>0–10 scale</td>
</tr>
<tr>
<td>Advanced care planning (ACP) completion</td>
<td>ACP</td>
<td>Patient and caregiver</td>
<td>Visit 3</td>
</tr>
<tr>
<td><strong>At study close</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QODD (if patient deceased)</td>
<td>Quality of dying and death</td>
<td>Caregiver</td>
<td>After patient death</td>
</tr>
<tr>
<td>End of life care trajectory</td>
<td>Chart Review Survey</td>
<td>Chart</td>
<td>At study close</td>
</tr>
</tbody>
</table>
preparedness in patients with IPF, a simple approach is used that involves asking patients to complete a numbered rating scale when answering two questions: 1) How well do you feel prepared for this disease? 2) How confident are you that your loved ones and clinician understand your wishes regarding care as your disease progresses? (1=not at all prepared OR not confident, 10=very well prepared OR very confident)

- **Advanced care planning preparation (ACP):** patients are provided with our institution’s advanced care planning tool and asked if they completed this ACP questionnaire (yes or no) and if no, provided with choices of why they did not complete.
- **QODD, V.3.2:** this captures the important domains of the QODD, as well as individual EOL preferences. By far, it is the most widely published and validated multi-item measure available for measuring QODD.31 This will be completed by the caregivers of patients who die during the course of the study.

**Data analysis plan**

Descriptive statistics will be used to present the patient characteristics. In each arm, rates of recruitment and retention will be presented and reasons for refusal will be obtained. Rate of recruitment and retention will be compared between two arms by χ² test. In interventional arm, total score from acceptability survey will be presented by median (IQR). Statistical assumptions (eg, normality) will be verified prior to hypothesis testing. This score will be tested for patients who retained in study versus who lost by Kruskal-Wallis test. We will compare the patients' demographic and clinical variables (obtained from electronic medical record (EMR)) between patients who were recruited in study versus who refused to participate in study.

Baseline characteristics of two arms will presented and compared. The knowledge questions will be measured on a scale of 1–10. We will provide descriptive statistics for each question as well as total score for each participant. In each arm, Wilcoxon signed-rank test will be used to determine differences in response to each knowledge question between visits 1 and 3. QOL and symptom burden will be measured for patients only, and preparedness perceived knowledge and stress will be measured for both patients and caregivers. We will test the effect of SUPPORT intervention (compared with control) on changes in knowledge score, QOL (and for each dimension), symptom burden and stress and preparedness using t-test for difference of score (between visit 3 and 1) between two groups. We will also apply mixed-effect models in which the intervention time interaction will assess the effect of intervention on score changes. In these models, the effect of intervention on each outcome will be adjusted for disease severity, comorbidity and demographic variables. Descriptive statistics will be used to present the QODD and EOL care trajectory results. Multiple imputations will be applied to impute missing data at visit 3 and complete cases analysis will be compared with all cases analysis. All analyses will be performed with intention-to-treatment analysis. P<0.05 will be considered statistically significant.

**DISCUSSION**

SUPPORT is a randomised controlled trial to test the efficacy of SUPPORT intervention compared with routine care in patients with IPF and their caregivers. The trial will evaluate whether the SUPPORT intervention decreases stress (primary outcome) for patients and caregivers, improves symptom burden, QOL, preparedness and advance care planning for patients and caregivers, QODD for caregivers if the patient dies during the course of the study as well as assess the impact of primary PC on healthcare resource use near the EOL.

PC, often the province of cancer care, is significantly underdeveloped in IPF, a disease which has a prognosis that is worse than many common cancers.32 The proposed study will provide objective evidence of a supportive care intervention delivered by clinicians early after diagnosis and the benefits when PCIs introduced early (following diagnosis). It will shift clinical and research paradigms to use primary PC to meet needs and then targeted referral to specialty PC when needed. Our long-term goal is to generalise the applicability of this intervention to other patient populations with non-malignant life-limiting illness such as heart failure and other advanced lung diseases, including chronic obstructive pulmonary disease, the third leading cause of death in the USA.

While PC has been a mainstay of cancer treatment, the integration of PC into non-malignant life-threatening disease is not routine; the literature continues to report that family members of decedents who received care at home with hospice services were more likely to report a favourable dying experience.25 The plan to integrate early PC into the care of patients with IPF and their caregivers is innovative and will substantially close the gap between patients with IPF and quality EOL care.

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**Contributors** KOL: conception of idea and design for this clinical trial, manuscript generation; MQR: contributed crucial intellectual content for design of this clinical trial, manuscript review and project oversight; MN: statistical guidance, manuscript review and contributed crucial intellectual content; KFG, DJC: contributed crucial intellectual content and manuscript review; MJK (research coordinator) and SK (nurse interventionist): both provided topic insight. All authors contributed to and approved the final version.

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**Competing interests** None declared.

**Patient consent** None.

**Ethics approval** The research protocol was approved by the University of Pittsburgh Institutional Review Board PRO16070539 and the trial is registered as NCT02929017 on clinicaltrials.gov.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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