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Case Report

Navigating social determinants of health barriers in the management of phenylketonuria☆

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ABSTRACT

Phenylketonuria (PKU) is an inborn error of amino acid metabolism that is typically identified by newborn screening. With lifelong treatment consisting of dietary management, frequent laboratory monitoring, and regular metabolic clinic visits, patients with PKU can maintain good health and metabolic control. Here, we describe the case of an 8-year-old patient with PKU who has been followed by a metabolic clinic since birth. Despite responsiveness to sapropterin, this patient has had periods of poor metabolic control throughout her life due to her family's economic hardships, including limited access to transportation, housing, food, and health insurance. This case illustrates how social determinants of health may negatively affect rare disease management and potential strategies for addressing barriers to care.

1. Introduction

Phenylketonuria (PKU) is an inborn error of amino acid metabolism caused by a deficiency in the enzyme phenylalanine hydroxylase (PAH; EC 1.14.16.1), which is responsible for the tetrahydrobiopterin (BH4)-dependent conversion of phenylalanine (PHE) to tyrosine (TYR). In PKU, pathogenic variants in the *PAH* gene (OMIM 261600) are inherited in an autosomal recessive manner and lead to PAH deficiency, resulting in elevated blood PHE and decreased blood TYR (Fig. 1). Significantly delayed or absent treatment of PKU causes severe and permanent cognitive impairment [1,2].

Early identification of PKU has been possible in the United States since the advent of newborn screening (NBS) in the 1960s [2]. Most affected individuals are identified and started on treatment within the first week of life. Management of PKU is challenging for patients and families since it involves a low-PHE diet, achieved by restricting natural protein through careful weighing, measuring, and tracking of food intake; the intake of medical formula to provide PHE-free protein and other essential nutrients; regular monitoring of PHE levels accompanied by detailed diet records (once or more per month); and regular follow-up with metabolic specialists and dietitians [6,7]. Metabolic stability of PKU is reflected by blood PHE and TYR levels within therapeutic ranges that help promote normal growth and cognitive development [2].

Treatment advances have enhanced the management and quality of life of individuals with PKU. First, a variety of medical formulas with increased palatability and portability aid in lifelong medical formula consumption. Next, low-protein modified foods have been developed to increase variety and provide a sense of normalcy within a protein-restricted diet [2,7]. Finally, sapropterin and pegvaliase are pharmaceutical options that can significantly aid in the metabolic control of PHE levels. Sapropterin is an oral medication that supplies BH4 and may enhance PAH activity in certain PKU phenotypes, while pegvaliase is an injectable enzyme substitution therapy for adults with PKU [2,8,9].

Although it is critical to initiate treatment in infancy to protect growth and brain development, children and adults with PKU need to continue treatment throughout their lives to avoid neuropsychiatric problems resulting from elevated blood PHE levels. Impaired executive functioning may occur with poor metabolic control, making it even more difficult for patients to carry out all aspects of PKU management. Optimal metabolic control is essential for individuals with PKU to maintain good health and quality of life, and they often require the support of their health care providers, family members, and peers to

Abbreviations: BH2, dihydrobiopterin; BH4, tetrahydrobiopterin; NBS, newborn screening; PAH, phenylalanine hydroxylase; PHE, phenylalanine; PKU, phenylketonuria; RD, registered dietitian; SDOH, social determinants of health; SNAP, Supplemental Nutrition Assistance Program; TYR, tyrosine; WIC, Special Supplemental Nutrition Program for Women, Infants, and Children..

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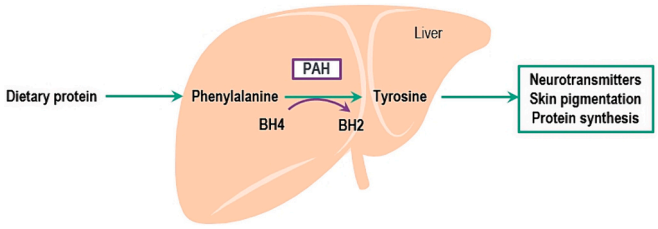

Fig. 1. Phenylalanine metabolic pathway.
Normal phenylalanine (PHE) metabolism involves the conversion of PHE to tyrosine (TYR) through the BH4-dependent enzyme PAH in the liver. TYR acts as a precursor for neurotransmitters, melanin, and endogenous protein synthesis. In PKU, deficiency of the PAH enzyme leads to elevated PHE and decreased TYR. High blood PHE levels are toxic to the brain, and low blood TYR levels impair the synthesis of TYR-related end products [3–5].
BH2, dihydrobiopterin; BH4, tetrahydrobiopterin; PAH, phenylalanine hydroxylase.

achieve this goal [2,6,10,11].

Despite the continued evolution of treatment strategies, PKU remains a chronic disease requiring complex management. Patients and their families are burdened by time-intensive and costly treatments necessary to manage the condition appropriately [12]. Patients with PKU describe social isolation, relationship issues, and emotional impacts related to their treatment regimen [6]. These factors create fatigue associated with PKU management; as a result, treatment adherence tends to decline as patients get older [10].

Barriers created by social determinants of health (SDOH) pose additional challenges to individuals with chronic diseases, including PKU. Food insecurity, housing instability, and financial hardships are common in the United States, and they negatively impact access to care and overall health. Poor health outcomes in people with chronic diseases may be exacerbated by SDOH-related issues [13].

Here, we present the case of a female pediatric patient with PKU identified by NBS. Despite the patient's response to sapropterin, her metabolic control has been negatively impacted by economic factors such as food insecurity, housing instability, and inconsistent transportation. This case demonstrates how the inherent burdens of PKU management can be compounded by SDOH-related barriers.

2. Case presentation

2.1. Patient presentation

The patient was diagnosed with PKU via NBS with an initial PHE level of 231 μmol/L on day of life 1 and a confirmatory PHE level of 869 μmol/L on day of life 5. After a 2-day washout period, the patient's PHE level decreased to 9 μmol/L. Her diagnosis was later confirmed by genetic testing revealing compound heterozygous variants in *PAH* of c.143T>C (p.Leu48Ser) and c.728G>A (p.Arg243Gln).

2.2. Social history

The patient's primary caregivers are her mother and grandmother. The patient's mother has 3 other children from 3 different partners, and 2 of the children (a minor half sister and 18-year-old half brother) are in the home and involved with the patient's care. The patient's father, who is not involved with the patient, has 4 other children from 2 different partners. None of the patient's half siblings have PKU; all are reportedly healthy. Additionally, there is no known family history of PKU, developmental delay, birth defects, or intellectual disability.

The patient and her family have faced multiple economic barriers to care since diagnosis. Her mother has been open about experiencing financial hardships, including housing instability. The family has a history of being unhoused, making multiple moves, and staying with the patient's grandmother. As a result, there have been challenges to providing the patient with medical formula and home monitoring supplies, both of which are critical to the daily management and ongoing monitoring of PKU.

2.3. PKU education

The patient's mother, grandmother, and older half siblings presented for an initial clinic visit on day of life 7, where they received education from the care team on PKU and its optimal management. During the initial clinic visit, the metabolic team provided the family with general education on PKU, inheritance/recurrence risk, and treatments. A simplified version of the metabolic pathway was drawn and explained to the mother. The registered dietitian (RD) taught the family how to measure and mix medical formula. They were provided with 3 cans of PHE-free formula, a gram scale, a mixer cup, and several educational materials on PKU in addition to a printed copy of the American College of Medical Genetics treatment guidelines. Potential treatment options for PKU, such as sapropterin, were briefly explained to the family. Blood spot collection was demonstrated, and filter papers and lancets were provided to the family for home blood spot collection. Phone numbers and email addresses for the nurse practitioner and RD were also provided to the family. The patient's family did not indicate any barriers to treatment during the initial clinic visit.

2.4. PKU monitoring and management

Immediately after the first clinic visit, the patient's family implemented a 2-day washout period when the patient was given only PHE-free medical formula according to the plan prescribed by the metabolic team. The significant reduction in the patient's PHE level indicates that the washout was successful [2]. The patient was then started on a diet prescription of medical formula combined with expressed breastmilk and standard infant formula (55 mg/kg/day of PHE, 2.5 g/kg/day of natural protein).

At 5 months of age, the patient completed a trial of sapropterin and was found to be responsive with a 75% decrease in plasma PHE. As a result, her dietary PHE allowance was increased from 265 mg/day to 347 mg/day (from 6.8 g/day to 7.4 g/day of natural protein).

The clinic has continued to follow this patient to present at 8 years of age; however, the frequency of clinic visits, laboratory draws, and home blood spot monitoring has been suboptimal (Fig. 2). In the past 18 months, she has been seen in the clinic once (vs the recommended 2 visits per year, or more frequently with variable metabolic control) and the family has submitted 5 home blood spot samples (vs the recommended 1 sample per month) (Table 1). The clinic has attempted to conduct more frequent visits, including the use of telemedicine; however, the family does not have reliable transportation or a stable internet connection for virtual visits. Phone visits have also been challenging since the patient's mother has had inconsistent mobile phone access. There have been 2 no-shows to the clinic in the past 18 months, and a telehealth visit was attempted but unsuccessful due to poor internet connection. Additionally, in the 18 months between visits, the family was unable to collect and send the requested number of blood spot samples due to housing insecurity.

The patient's diet prescription, protein allowance, and sapropterin dosage have continued to be adjusted based on her plasma PHE levels and growth needs. At age 8 years, her prescribed regimen includes 200 mg/day of dietary PHE (0.1 g/kg/day; 4 g/day of natural protein) and 40 g/day of protein from medical formula, with 1 serving of formula to be consumed immediately before each meal. She reports taking her full medical formula prescription only 2 to 3 days per week, and she takes 2 h to finish 1 serving of formula. It is possible the patient's dietary PHE tolerance is higher than her prescription, but the family does not carefully track PHE intake or collect blood spot samples frequently enough to make this assessment. Although counting milligrams of PHE is

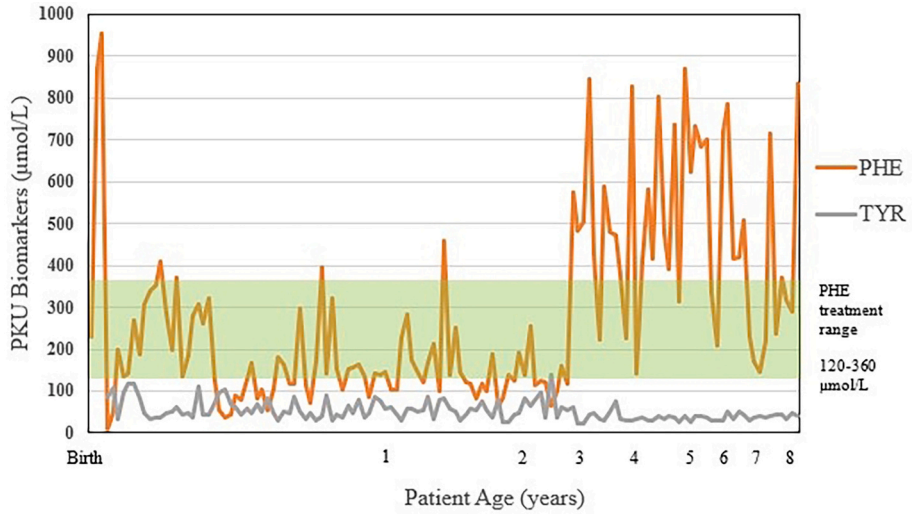

Fig. 2. All biochemical laboratory test results for blood samples collected from the patient via home blood spot monitoring or plasma amino acid draws in the clinic from birth to present. Data points above the shaded area indicate blood PHE levels higher than the treatment range.
PHE, phenylalanine; PKU, phenylketonuria; TYR, tyrosine.

Table 1
Recent biochemical laboratory test results for blood samples collected from the patient via home blood spot monitoring or plasma amino acid draws in the clinic.

PKU biomarkers (treatment range)	3 months before the present	4 months before the present	7 months before the present	11 months before the present	14 months before the present	16 months before the present
PHE, µmol/L (120–360)	836**H**	290	319	372**H**	238	714**H**
TYR, µmol/L (35–110)	40	46	32**L**	43	43	41

PHE, phenylalanine; PKU, phenylketonuria; TYR, tyrosine.
H indicates PHE higher than the treatment range, and **L** indicates TYR lower than the treatment range.

recommended for optimal metabolic control, the family looks at food labels for grams of protein and gives the patient foods with 0 or 1 g of protein per serving. If a food has 2 g of protein on the label, the patient gets a smaller serving; if it has 3 g of protein or more, she is not given the food. The patient knows where her family keeps higher protein foods, and her mother has caught her climbing on the counter to access foods that have purposely been put out of her reach. The patient has also admitted in clinic visits to sneaking foods like chips and cake.

The patient's compliance with sapropterin seems to be the most consistent element of her PKU management regimen. Her mother reports that she rarely, if ever, misses a dose. However, insurance coverage lapsed after the most recent clinic visit, and the patient did not receive her medication for 2 weeks. This lapse was not communicated to the clinic in enough time to provide assistance. The patient's mother reported difficulty in signing electronic paperwork to renew insurance coverage, and transportation problems prevented her from presenting to the office to sign paperwork in person. The 2-week period without sapropterin is reportedly the longest the patient has gone without the medication since she started it. Given the patient's robust sapropterin response, the lack of medication contributes to poor metabolic control; therefore, sapropterin is considered to be a crucial element in her PKU management.

2.5. Barriers to care and support services

Several barriers have hindered the patient's ability to follow up in the clinic at the recommended frequency. First, the family lives approximately 40 miles from the clinic, and their access to reliable transportation is inconsistent. The family's car has broken down frequently and clinical staff have often not been made aware of an issue until an appointment was canceled. Although public transportation tokens are available from the clinic's social workers, attempts to contact the family regarding this issue have thus far been unsuccessful. Next, the patient's mother has had a variable employment status, with frequent job changes and travel away from the home. Although telehealth options have been offered to the family, lack of reliable internet access has prevented them from utilizing this option. Finally, the clinic has had difficulty keeping in touch with the family due to frequent phone/phone number changes.

Another barrier to metabolic control has been access to foods low in PHE. Financial hardships have led to moderate food insecurity for the family. The patient's insurance does not cover low-protein modified foods, and the foods available at home are higher in PHE. Despite assurance that clinic staff could help with dietary accommodations in Utah public schools, the patient's mother chose homeschooling due to concerns that the patient would not follow her low-protein diet. As a result, the patient does not benefit from the child nutrition programs available in formal school settings. National school meal programs provide nutritionally balanced meals that are low-cost or free to students who qualify based on household income [14]. These meal programs are required to accommodate medical conditions necessitating a special diet; therefore, children with PKU have the opportunity to receive low-protein modified foods regardless of insurance coverage [15]. The lack of access to adequate and appropriate foods may be a factor in the patient's variable metabolic control.

The patient's grandmother and 18-year-old half brother are responsible for her homeschooling. Her cognitive development is reportedly normal; however, the state of Utah does not impose requirements on instruction or attendance [16]. As a result, she is not subject to any academic testing and does not have access to any supportive resources that might be needed (eg, an Individualized Education Plan). Because PKU increases the risk of cognitive and psychological problems, the metabolic team recommends that all patients with PKU undergo formal

neurocognitive testing at regular intervals throughout childhood and adulthood [2]. The patient had a brief meeting with the clinic's psychologist at 18 months old; however, due to repeated missed clinic visits, she has never completed any formal cognitive testing.

The patient is eligible for state programs that support PKU management. She is insured by Medicaid, which covers the cost of her clinic visits and medication. She is also eligible to receive her medical formula free of charge, provided by the state for individuals with PKU up to 18 years of age. The clinic staff has supported the family by ordering medical formula on their behalf and having supplies sent to the grandmother's address. The clinic is also able to facilitate support through patient outreach events; however, the patient and her family have not participated in any of these events, presumably due in part to lack of transportation. Because networking between patients and families affected by PKU can help overcome barriers to management, the patient's family has been connected with multiple other local families managing PKU, though it is unclear if any relationships have been developed.

3. Materials and methods

Medical records and clinical parameters were reviewed by the treating clinical team. Informed consent was obtained from our patient's mother for publication of this case.

4. Discussion

Although treatment advances continue to improve rare disease outcomes, there are disparities in care for patients who are negatively affected by SDOH [17]. PKU is a noteworthy example of a condition that has historically caused profound disability due to the absence of identification and treatment, but now it can be successfully managed with early identification and lifelong treatment. Patients with PKU who have economic challenges can have difficulties accessing care, leaving them susceptible to severe physical, cognitive, and behavioral problems that could have been prevented [18].

Access to transportation is considered a major SDOH and has been a prominent barrier to care for the patient presented in this case. Data from the National Health Interview Survey (1997–2017) revealed that in 2017, 5.8 million people in the United States postponed medical care due to lack of transportation. Those living below the poverty line and/or receiving Medicaid benefits were more likely than other demographic groups to cite transportation as a barrier to care. Although individuals who live in major metropolitan areas are more likely to have public transportation available, transit time and finances can prevent utilization [19]. Interventions have been proposed to mitigate the impacts of transportation barriers on health care. First, screening tools can be used to identify transportation insecurity in clinical settings. These tools range from in-depth evaluations to simple yes/no questions that may be more feasible to implement in busy health care settings. While more work is needed to better capture these barriers, some health systems have begun utilizing screening tools [20]. Once transportation barriers are identified, evidence-based interventions can be offered, including the provision of public transit passes, transport vouchers, or travel reimbursement; arrangement of transportation services; or free shuttle services. These interventions have been found to be most beneficial to health outcomes when combined with other interventions such as care coordination, education, and counseling. Community health workers, social workers, nurses, and other clinical staff are helpful for implementing these interventions [21].

Housing insecurity, which includes cost burden, frequent moves, and homelessness, has detrimental effects on overall health and well-being [22]. In 2021, the Center for Economic and Policy Research reported that 1 in 5 US households experienced housing insecurity. Nearly 1 in 3 households with children had housing insecurity, with gaps increasing between White households and Black, Hispanic, and other households after the COVID-19 pandemic [23]. Children are disproportionately affected by housing insecurity and are at risk for poor growth, development, and health status. Families affected by housing insecurity frequently have challenges accessing medical care, so children with long-term health care needs such as our patient with PKU are particularly vulnerable [24]. Housing insecurity is a complex issue that requires the collaboration of government and private stakeholders; however, health care organizations are becoming increasingly involved in addressing the crisis, with payors beginning to invest in affordable housing initiatives [25]. Medical providers can help identify patients with housing insecurity through screening tools, and they can potentially document a diagnosis code for patients experiencing homelessness in medical records. This can be a first step to connecting at-risk patients with appropriate support systems such as social workers, counselors, and housing services [26].

Food insecurity is described as inadequate or inconsistent access to food and is an SDOH that affected 13.8 million US households in 2020 [27]. Food insecurity often occurs in tandem with housing insecurity and is independently associated with poor health, delayed development, and nutrient deficiencies in children [24]. Considering that the cornerstone of PKU treatment is careful adherence to a special diet, food insecurity can be a serious threat to metabolic control. While medications and medical formula for PKU are likely to be covered by insurance, costs for low-protein modified foods are typically out of pocket. It has been reported that low-protein modified foods cost 2 to 8 times more than unmodified foods, making them extremely difficult to obtain for many individuals, especially those experiencing economic hardships or food insecurity [18,28]. A 2020 pilot study found that females with PKU experience food insecurity at a rate of 2 to 4 times higher than the general US population. Compared to females with PKU who had higher food security, those experiencing food insecurity consumed more dietary PHE and less medical formula. The authors inferred that individuals with PKU who have financial struggles may be unwilling or unable to spend money on their medical and dietary needs. As with other SDOH, an important step for clinicians is to screen patients and assess gaps in food access. Given that dietary evaluation of patients with PKU is a central component to metabolic clinic visits, metabolic dietitians should screen patients for food insecurity and be prepared to provide resources to those at risk. Patients and their families can be referred to local food banks with recommendations for low-PHE food options such as canned fruits and vegetables, fruit or vegetable juices, or certain refined grain products that can fit the PKU diet when carefully measured (eg, instant white rice or gluten-free grain items). Additionally, clinic staff can coordinate with food assistance programs such as the Supplemental Nutrition Assistance Program (SNAP) and the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) to ensure patients are able to receive appropriate foods for the PKU diet [18]. Finally, families managing PKU can benefit from connecting with local and national PKU advocacy groups, patient support groups, low-protein modified food manufacturers, and medical formula assistance programs. These entities can provide direct and indirect support for patients with PKU experiencing food insecurity and a variety of other issues related to PKU management.

Health literacy, defined as “the degree to which individuals have the capacity to obtain, process, and understand basic health information,” is another SDOH that can present risks or benefits to patients. Low health literacy is typically associated with lower levels of education, lower economic status, and negative impacts to chronic disease management and outcomes [29]. In the case of our patient's primary caregivers, their level of education is unknown, and their health literacy is estimated as low to average. Despite this assumption, the caregivers have demonstrated understanding of PKU management principles since the patient's diagnosis. Adherence to instructions for PHE washout after the NBS visit and overall consistency with medication administration indicate that the caregivers have been able to comprehend and implement concepts taught to them in clinic despite various barriers. A large proportion of

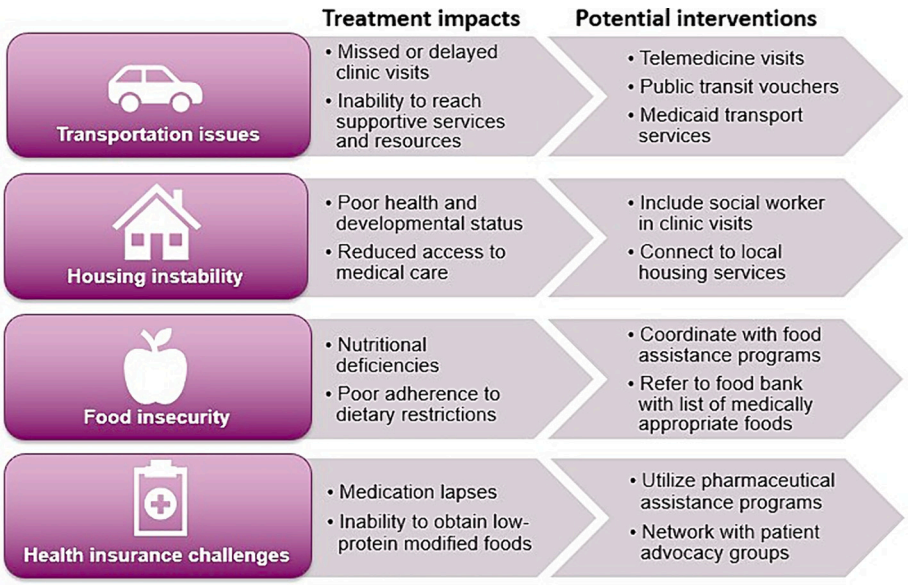

Fig. 3. SDOH-related barriers, treatment impacts, and potential interventions for a patient with PKU.

the US population has limited health literacy, which has a significant impact on patient outcomes [29]. As such, we recommend that metabolic teams consider health literacy when working with patients regardless of their perceived education level or economic status.

Health care providers should be aware of how SDOH can affect their patients, especially those with rare diseases such as PKU, given the frequency of SDOH barriers in the general population and their detrimental impacts on medical access and health outcomes (Fig. 3). Use of SDOH screening tools at our patient's initial clinic visit may have identified her family's barriers early and provided an opportunity for referral to appropriate resources. Outreach to the family became more difficult as time elapsed; early intervention may have aided in keeping them connected to the clinic. Additionally, the expertise of an embedded social worker within the metabolic clinic would have been valuable to help the patient's family access transportation, housing, and other assistance programs. Currently, social workers are not embedded within our clinic, and their services are available only on a case-by-case basis. Social work consultation has been requested on multiple occasions for this patient; however, missed clinic visits have prevented those consultations from occurring. Calls from social workers to the family have also been attempted but unsuccessful. Since metabolic clinicians already face time and staffing challenges, this case is a prime example of how a dedicated social worker could help address SDOH more directly while enabling dietitians, physicians, and advanced practice providers to focus on medical management [30]. While further research is needed to assess the impacts of SDOH on the management of PKU, this case illustrates the importance of awareness and persistence on the part of the metabolic team to ensure that patients with SDOH barriers have the best possible outcomes.

Consent for publication

Informed consent was obtained from the patient's mother for this work.

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Author statement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We understand that the Corresponding Author is the sole contact for the Editorial process. She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

CRediT authorship contribution statement

Ashley Andrews: Writing – review & editing, Writing – original draft. **Kate McMinimee:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

AA has participated in advisory boards and/or received honoraria from Amgen Inc., Acer Therapeutics, and Sanofi. KM has no declarations.

Data availability

No data was used for the research described in the article.

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