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Unmet needs in inflammatory bowel disease

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ABSTRACT

Despite the recent developments in the diagnosis and management of inflammatory bowel diseases (IBD), patients still suffer from disabling bowel symptoms and significant disease complications and many questions remain to improve their care. IBD is a chronic disease, whose management could be divided into the five different stages of chronic diseases, ranging from the pre-treatment evaluation phase to the induction therapy, maintenance therapy, monitor and re-establishment of control and the cessation of the disease. Reconciling these phases with the current unmet needs in IBD could help tailor priorities for research. In this review, some of the unanswered questions in the management of both Crohn's Disease and Ulcerative Colitis will be addressed, by following this paradigm of chronic diseases' management.

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD), that can lead to disabling bowel symptoms and progressive bowel damage (Torres et al. 2017; R. Ungaro et al. 2017). Being diagnosed at a young age, patients frequently require long-term chronic medications and may experience complications such as hospitalizations and surgery (Torres et al. 2016).

Despite great advances in the modern management of IBD with the introduction of new effective drugs, adoption of stricter endpoints, and use of better treatment strategies, there remain many unmet needs. Identification of these unmet needs, aligned with the different stages of chronic disease management, may help tailor priorities for research, to improve physicians' therapeutic approach and overall clinical care for IBD patients (Fig. 1).

1.1. Unmet need 1: Better risk stratification of IBD patients

The acknowledgement that chronic inflammation in IBD ultimately results in poor outcomes has led to a paradigm shift, where it is accepted that early intervention with more advanced therapy may prevent disease progression and avoid complications (D'Haens et al. 2008; Schreiber et al. 2013; Schreiber et al. 2010; Colombel et al 2010; Khanna et al. 2015). Moreover, it has been demonstrated that early biologic treatment is associated with improved clinical outcomes and, therefore, the accurate identification of patients who should receive early intervention with highly effective therapy is a key need (R.C. Ungaro, Aggarwal, et al. 2020; Hamdeh et al. 2020). However, treatment of all patients upfront with biologics, combination therapy or with the newer small molecules, not only is costly but also may expose those with an indolent disease course to unnecessary risks of therapy. Therefore, the challenge remains to be able to predict those patients who will benefit most from early intensive therapy, while sparing those who will derive minimal benefit from such treatment (Devlin et al. 2012).

Although international associations have proposed indices and clinical decision support tools to help clinicians identify higher-risk patients, risk stratification according to clinical features alone can still be challenging (Siegel et al. 2018; W. J. Sandborn, 2014; Nguyen et al., 2020). More objective and prospectively validated biomarkers are thus needed to allow for a precision-medicine approach in IBD (B. Verstockt et al. 2021).

The RISK study is an example of an observational prospective study that revealed important prognostic findings in treatment-naïve, newly diagnosed paediatric Crohn's disease patients allowing for the development of a risk stratification model combining age, race, disease location, antimicrobial serologies, and ileal gene signatures for the prediction of disease complications (Kugathasan et al. 2017). However, this model still lacks validation in independent paediatric and adult cohorts and may be challenging to implement in practice due to its multimodal nature. The PROSPECT tool (clinical, serological, and genetic variables) and the

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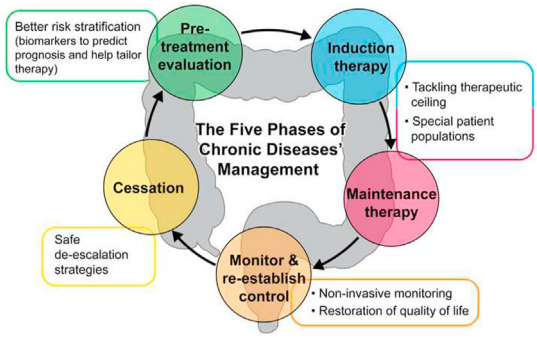

Fig. 1. The five phases of chronic diseases' management and unmet needs in IBD; *adapted from* (Glasziou et al., 2005).

PredictSURE IBD® (immunological markers) are other examples of prognostic tools used to predict outcomes in CD and IBD, respectively (Siegel et al. 2016; Biasci et al. 2019).

Ultimately, the prediction of disease severity through biomarkers that will help effectively guide treatment selection will involve the use of multiple complementary approaches, such as blood-based serologic and genetic tests, proteomic, metabolomic or metagenomic and radiomics or imaging-based biomarkers, contributing to the development of the IBD interactome. By promoting the understanding of specific physiological phenomena associated with prognosis, it is hoped that a multi-omics approach will allow for more tailored risk stratification of IBD patients (B. Verstockt et al. 2021). Indeed, some precision medicine trials are already ongoing. The PROFILE trial is a prospective trial that intends to stratify patients using a CD8T cells signature and to evaluate treatment response according to a "step-up" or "top-down" approach (Parkes et al. 2018). The COMPASS-CD is another trial that intends to assess the role of CDPATH™, a blood biomarker-based tool to help predict the development of CD related complications within 3 years (NCT04809363). Hopefully, in the future, such tools will be widely available to help predict disease course and risk-stratify patients.

1.2. Unmet need 2: Choosing the best therapy for the individual patient

IBD is a heterogeneous and multi-phenotypic disease, with significant differences in disease location, disease activity, disease presentation and disease course in each patient. Despite this heterogeneity, current treatment algorithms suggest a standard approach to all patients, without considering the individual and molecular specificities of the disease nor individual patients' risk factors for therapy-related complications. With the expanding therapeutic arsenal available, it is clear that IBD treatment needs to move away from a "one size fits all" approach, and there is a pressing need to identify biomarkers that could predict response to therapy or therapy-specific complications. Stratifying patients based on their molecular phenotyping could help select the most appropriate first-line therapy and identify patients at higher risk of severe adverse events with certain medications, leading to personalized IBD care (B. Verstockt et al. 2021). In the absence of these precise biomarkers, identification of high-risk features and their incorporation into a clinical decision tool may help select the most adequate therapies according to the probability of achieving clinical remission and the time needed to achieve a response (W. J. Sandborn, 2014).

Even if in its early stages, recent research has identified some biomarkers that could drive therapeutic choice. An important step towards this goal will include more frequent incorporation of exploratory biomarkers in the early phases of clinical trials and an assessment of the ease of implementation of those biomarkers in routine care (B. Verstockt et al. 2021).

For example, the PANTS study demonstrated a significant association between HLA-DQA1*05 and the development of antibodies against anti-TNF agents, although further randomized controlled biomarker trials are required to determine whether pre-treatment testing for HLA-DQA1*05 may improve patient outcomes (Sazonovs et al. 2020). In another study, a single cellular module consisting of IgG plasma cells, inflammatory mononuclear phagocytes, activated T cells, and stromal cells (GIMATS) in the inflamed tissue at diagnosis was found to be predictive of anti-TNF therapy failure in patients with CD (Martin et al. 2019). Other relevant biomarkers that seem to predict failure to anti-TNF drugs are Oncostatin M and Triggering Receptor Expressed in Myeloid Cells-1 [TREM1], although conflicting results have been published regarding the latter (West et al. 2017; Gaujoux et al. 2019; B. Verstockt, Verstockt, Dehairs, et al. 2019c; B. Verstockt, Verstockt, Blevi, et al. 2019b). Moreover, through a multiomics approach, Verstockt et al. also identified transcriptomic and proteomic predictors of response to ustekinumab (B Verstockt, Sudahakar, et al. 2019a).

Despite the identification of these biomarkers, their incorporation in routine care for risk stratification and tailored therapy selection is not yet established, but urgently needed.

1.3. Unmet need 3: Therapeutic ceiling and treatment sequencing

Despite the current array of treatment options in UC and CD, remission rates in induction trials are still less than 50%, revealing a therapeutic ceiling in the management of both diseases and potential challenges that need to be addressed (Danese et al. 2019; Colombel et al. 2017a,b). Even when implementing early individualised optimized therapy in the CALM study, up to 1/3 of the patients developed complications over 3 years (R.C. Ungaro, Yzet, et al. 2020). This is the reason why current treatment goals have become more demanding, to allow for more stringent control of inflammation and limitation/prevention of bowel damage. A treat-to-target approach with tight monitoring has been advocated to improve drug efficacy (Turner et al. 2021). However, there is a disconnect between these treatment goals and what can be achieved in clinical practice, according to the timing of diagnosis of the disease, timing of initiation of treatment and the therapeutic armamentarium available. Also, the time to achieve a specific target may change with different therapies and particularly for transmural and histological healing, the time needed to achieve these targets is not yet established (Turner et al. 2021). The VERDICT trial (NCT04259138), which is ongoing, aims to determine the optimal treatment target and the time for its evaluation in UC.

Moreover, it is important to understand that treatment targets need to be considered as a whole so that physicians do not go through the risk of cycling through therapies if full endoscopic healing was not attained despite significant patient and biomarker improvement. Besides, after failing a first biologic therapy, response to a second biologic is usually inferior (Alsoud et al. 2021). Therefore, new, and more effective therapies for IBD are needed. Apart from the possibility of developing new and more precise drugs, many questions regarding the already approved therapies persist, such as which drugs should be used in which sequence, when to start a drug, how to best adjust dosing and when to stop.

Most of the comparative efficacy data available to date has been retrieved from systematic reviews and network meta-analysis (Singh et al. 2018). Head-to-head trials are already implemented in other fields such as Oncology. However, in IBD they are in their early development, mostly due to the challenges related to their complex study design and intricate execution. Specific training to IBD specialists would ease their employment and would allow going beyond the simple comparison of two drugs to include biomarkers that could help stratify patients, advocating for a more personalized treatment strategy. The VARSITY trial compared the efficacy of vedolizumab against adalimumab in the treatment of moderate to severe ulcerative colitis, and the SEAVUE trial, compared ustekinumab to adalimumab as an induction and maintenance therapy in moderate to severe biologic naïve CD (Irving et al. 2021). These trials can help to position drugs in the treatment landscape, but more direct comparison trials are needed in the field, especially with the introduction of small molecules in the therapeutic armamentarium

(Pouillon et al. 2020; William J. Sandborn et al. 2020).

Apart from selecting the most appropriate drug, one possible treatment strategy could also involve the combination of different mechanisms of action to tackle distinct mechanisms of disease. There is already the precedent of combining therapies in IBD, such as oral and rectal formulations of 5-ASA, steroids with other drugs, and combination therapy of infliximab plus azathioprine that have been demonstrated to be superior to each of these drugs individually. (Colombel et al. 2010; Panaccione et al. 2014) Theoretically, the use of two different drugs with different mechanisms of action has the possibility of acting in different phases of the inflammatory cascade, increasing the possibility of controlling inflammation and avoiding possible mechanistic escapes and loss of response. Moreover, the combination of two different therapies may allow the possibility of synergy between the two drugs and potential specific time-sequences (eg. small molecules for induction and biologics for maintenance). However, data on combination therapy in IBD is still limited. In a recent systematic review and meta-analysis of 288 trials of dual biologic or small molecule therapy, the rates of endoscopic remission were still inferior to 40%, possibly because combination therapy with biologics and/or small molecules are usually reserved for the treatment of highly selected, refractory IBD patients at specialized centres (Ahmed et al. 2021). Aside, from this limited data on superior efficacy, safety concerns regarding the increased immunogenicity of combining strategies still exist, as was also demonstrated in other immune-mediated diseases (Hirten et al. 2018). Therefore, further randomized clinical trials (RCT) on combination therapy are needed, whose evaluation should be focused on risk-safety and cost-benefit analysis.

1.4. Unmet need 4: Treating special patient populations

1.4.1. The patient with Perianal disease

Despite current advances in surgical and medical treatment, the long-term healing rate of perianal fistulas remains disappointing, with significant recurrence rates, particularly in complex fistulas, which account for most of the fistulas in CD (Molendijk et al. 2014). In terms of medical treatment, infliximab is the best-studied drug for the treatment of perianal fistulizing CD, although recent retrospective studies and post-hoc analysis have also demonstrated a role for vedolizumab and ustekinumab (Schwartz et al. 2021; Attauabi et al., 2021). However, it is important to highlight that all these therapies have healing rates that do not surpass 50% and new emerging drugs directed to perianal CD are needed (Chapuis-Biron et al. 2020; Lopez et al., 2019). An example is a phase II clinical trial on the role of the JAK 1 inhibitor, Filgotinib, in perianal CD, whose results are eagerly awaited (NCT03077412). The combination of biological therapies is also a relevant unaddressed topic in perianal CD, with observational studies suggesting positive results (Huff-Hardy et al. 2017).

One of the most promising treatment modalities in perianal CD, that will probably significantly change the management of this disease in the coming years, is mesenchymal stem cells (MSC). They act through a reduction on the inflammatory burden of the fistula tract and further studies are needed to evaluate their therapeutic role, particularly in patients with proctitis, that were initially excluded from the trials (Rackovsky et al. 2018).

Finally, regarding the role of surgical and medical care, only recently, the PISA-II trial, a patient preference RCT compared the efficacy of surgical closure following anti-TNF induction to anti-TNF therapy without surgery. This study demonstrated that surgical closure following anti-TNF induction treatment induces MRI healing more frequently than anti-TNF alone, leading to increased long-term clinical closure and reduced recurrences. Therefore, patients amenable for surgical closure should be counselled for this therapeutic approach(Meima - van Praag et al. 2021).

With the standardization of the therapeutic outcomes in perianal fistulizing CD, further head-to-head trials comparing the available therapeutic options and their combination will be possible.

1.4.2. Refractory UC proctitis

Ulcerative proctitis (UP) is defined as a disease limited to the rectum, that occurs in approximately 30% of UC patients at diagnosis (Danese et al. 2019). Some UP patients are refractory to standard medical therapies and there is little evidence on further management of this disease. Furthermore, UP patients are systematically excluded from biologics RCT and, therefore, there is limited information on the efficacy of these drugs in these patients. Recently, a retrospective French cohort study with 104 patients evaluated the efficacy of anti-TNF therapy in patients with refractory UC and demonstrated that it induced clinical remission in 50% of the patients and mucosal healing in 60% (Pineton de Chambrun et al. 2020). Nevertheless, more prospective studies with adequate sample size and power are needed to evaluate the role of different biologic therapies in refractory UP patients.

1.4.3. Treating the elderly patient

The incidence and prevalence of IBD in the elderly continue to grow, partly reflecting an ageing global population. The presence of comorbidities and increased frailty in this population and the risk of development of more significant adverse events has led to sub-optimal IBD therapy in the elderly, evidenced by elevated chronic corticosteroid use and surgical rates. Moreover, elder IBD patients are almost always excluded from RCTs of biologic therapies and therefore the safety of these drugs in this population is undetermined, further limiting their use (Ananthakrishnan et al. 2017). The use of gut-selective immunosuppressants would theoretically be of interest in elder IBD patients, but further studies assessing its efficacy and safety are needed.

Additionally, treatment targets in the elderly differ from the general population and should probably be less tight and adapted according to the patient's performance status, life expectancy and personal preferences (Ananthakrishnan et al. 2017). Non-invasive monitoring should also be increasingly implemented to avoid the risk of consecutive endoscopic assessments.

In summary, further studies to identify risk factors for a more aggressive disease course in older-onset IBD and to evaluate the safety of current treatment options are needed. This could allow for the development of a treatment algorithm in elder IBD patients that includes prognosis stratification and a balance between the risks and the benefits of escalating therapy and improving long-term outcomes. New modified treatment targets should also be included in this algorithm, with the consideration of functional objectives, such as the preservation of physical status and functional independence.

1.4.4. Post-operative recurrence prophylaxis

Prevention of post-operative recurrence (POR) is still a controversial field. A recent systematic review and meta-analysis intended to compare the effect of different medical therapies in POR prophylaxis demonstrated that anti-TNF therapies alone, or in combination, appear to be the best medications for preventing endoscopic recurrence. However, the role and best timing to initiate biologic therapy in the post-operative setting, as well as the positioning of new biologic therapies, is still to be determined. Furthermore, medical prophylaxis is not completely harmless and prescription should be cautious to restrict medical therapy to those most at risk, avoiding undesired and potentially serious adverse effects (Burr et al. 2019). In the future, further robust studies are needed to identify previously operated CD patients at increased risk of POR, contributing to the development of a clinical algorithm where different prophylactic strategies may be defined according to a multifactorial risk score assessment.

1.5. Unmet need 5: Better monitoring

Current time-bound algorithms in IBD imply a regular assessment of disease activity to identify early failures in therapy so that treatment can be adapted to achieve long-term remission. Although IBD diagnosis will probably continue to rely on invasive procedures such as colonoscopy,

ongoing disease monitoring is increasingly focused on non-invasive strategies, to avoid the costs and inconvenience for patients of performing repeated colonoscopies and to improve adherence to a tight-monitoring strategy.

To date, the most frequent parameters used to monitor disease response are clinical symptoms, inflammatory markers (including faecal calprotectin and C-reactive protein (CRP)), endoscopic scores, and cross-sectional imaging. According to the STRIDE II consensus (Turner et al. 2021), clinical response is considered an immediate goal in IBD, clinical remission and normalization of serum and faecal markers are both intermediate goals and endoscopic healing and restoration of quality of life and absence of disability are long-term targets. Transmural healing for CD and histological healing for UC are considered desired goals, but not formal targets for disease management, as more studies are needed to evaluate the risk/benefit of these objectives and clearer definitions for both outcomes are required.

For patients, clinical symptoms are usually the most significant parameter to control. However, their correlation with the degree of mucosal inflammation in CD is poor and therefore, it is not infrequent to encounter completely asymptomatic patients with significant mucosal inflammation. Therefore, endoscopic healing (EH) in CD is a more significant target than clinical remission and a composite strategy including clinical and biochemical biomarkers seems more effective to monitor EH than clinical monitoring alone (Colombel et al. 2017a,b). Moreover, clinical scores are mostly subjective and symptoms of irritable bowel syndrome (IBS), which are often concomitant may lead to an overestimate of disease activity. As opposed to CD, patient-reported outcomes (PROs) in UC seems to strongly correlate with endoscopic activity, particularly if a combination of rectal bleeding (RB) and stool frequency (SF) is used (Restellini et al. 2019; Colombel et al. 2017a,b).

Regarding biomarkers' use in non-invasive monitoring, although CRP does not seem to correlate with disease activity assessed by clinical scores in ulcerative proctitis and prediction of post-operative recurrence, it does seem to correlate with transmural inflammation in CD, with endoscopic activity in left-sided UC, and with the prediction of clinical relapse and therapeutic failure (Dragoni et al., 2021; Ma et al. 2019). However, it is not established to which extent CRP variation can be used to predict response to therapy in these selected populations of patients. On the other hand, faecal calprotectin (FC) also seems to predict histological remission in UC, although a standard cut-off is not yet established (D'Amico et al. 2020). The CALM study demonstrated that the combined use of clinical symptoms, FC and CRP to escalate anti-TNF therapy allows for better outcomes in CD (Colombel et al. 2017a,b). However, the extent to which we can account for serum and faecal biomarkers to allow for escalation of therapy without needing endoscopy is still to be clarified.

Cross-sectional imaging has also been increasingly used in combination with biomarkers and has been assessed as an alternative to colonoscopy for non-invasive monitoring. Intestinal ultrasound (IUS) is an easily accessible, inexpensive, and very well-tolerated technique, that can be performed at the bedside for the evaluation of bowel inflammation. Although its accuracy seems lower for disease proximal to the terminal ileum or involving deeper pelvic loops, previous studies have already demonstrated a similarity between IUS and magnetic-resonance enterography (MRE), which is the gold standard for the evaluation of the small bowel (Panés et al. 2011; Horsthuis et al. 2008, 2009; Puylaert et al. 2015; Taylor et al. 2018; Calabrese et al., 2018). In terms of guiding clinical decisions in CD, the accuracy of IUS also seems comparable to that of MRE (Allocca et al. 2018). However, before it is used in a treat-to-target strategy, further studies clarifying the role of transmural healing as a new target for CD are needed. The development of validated and standardized IUS indexes is also necessary (Sævik et al. 2021). Although less implemented in clinical practice, IUS can also be used to monitor disease activity in UC (Maaser et al. 2020). The Milan Ultrasound Criteria (MUC) was recently developed and externally validated and can be used to accurately assess UC activity (Allocca et al. 2021).

Another relevant stone of non-invasive monitoring is the use of therapeutic drug monitoring (TDM), which has already been shown to be useful in the management of IBD patients (Kennedy et al. 2019; Vande Casteele et al. 2015; Assa et al. 2019). However, limitations to TDM use also exist, namely the identification of the optimal thresholds for drug concentration, which may vary according to the type of administration (subcutaneous versus intravenous), disease severity and phenotype (fistulizing disease seems to need higher levels of drug), patient profile (including body weight, gender and body composition), type of IBD (UC patients seem to need higher drug levels when compared to CD patients) and the endpoint that is being targeted (clinical versus endoscopic remission). The PRECISION trial is an example of an RCT that tried to use computer-based systems to tailor drug monitoring and is probably an example of the future of TDM strategies, as drug level thresholds need to be modulated according to different variables that are drug, disease and patient-related and may ultimately depend on the intended treatment target (Strik et al. 2021).

After addressing some of these unmet needs in non-invasive monitoring, the most suitable strategy for tight monitoring may eventually rely on a combination of biomarkers, cross-sectional imaging and TDM.

1.6. Unmet need 6: Restoring quality-of-life

Restoration of quality of life should be the ultimate long-term outcome in IBD management. Although disease remission can be achieved, some bothersome symptoms can still prevail, limiting the achievement of this goal. Fatigue is a common symptom in IBD patients that can be present in more than half of the patients with quiescent moderate-to-severe disease (Villoria et al. 2017). Moreover, most of these patients suffer from anaemia, which also leads to fatigue, with a negative impact on quality of life (Danese et al. 2014). Despite this, much is unknown regarding fatigue's pathophysiology, limiting the possibility of offering targeted treatment. Further prospective pharmacological and non-pharmacological trials are needed, alongside patients and physicians' education on the subject. Anxiety and depression also affect around one-fifth of patients with IBD and therefore psychosocial interventions directed to these patients are also needed (Neuendorf et al. 2016).

1.7. Unmet need 7: When and how to de-escalate

Another relevant question not yet answered in IBD care is related to the possibility of safe de-escalation of therapy once remission is achieved. Although biologics have changed the paradigm of care in IBD, some concerns related to safety, direct and indirect costs, special situations and patients' preferences have led to the evaluation of the possibility to de-escalate therapy or provide some drug "holidays", particularly from biologics.

The STORI trial was the first prospective study intended to assess the risk of relapse after infliximab therapy discontinuation in patients on combined maintenance therapy with antimetabolites for at least one year and in corticosteroid-free remission for at least 6 months. According to this study, approximately 50% of the patients experienced a relapse in the first year after stopping therapy, though the majority had effective and well-tolerated re-treatment with infliximab (Louis et al. 2012). Similar results were found after 7 years of follow-up of this cohort, where around 20% of the patients did not restart infliximab nor developed a major complication and 70% were considered to have a successful de-escalation strategy, defined by the absence of failure to infliximab restart and no major complication (Reenaers et al. 2018). Although the STORI trial has highlighted some clinical and biochemical markers to identify patients in remission with a low risk of relapse after infliximab withdrawal, high-quality data from ongoing RCTs, such as the SPARE trial (NCT02177071) in CD patients and the BIOSTOP trial (NCT03011268) in UC patients, are eagerly awaited, as safe de-escalation strategies should also follow a personalized approach, with the identification of specific patients' characteristics or molecular patterns that

could help stratify the risk of recurrence. Until those clinical and biologic markers are identified, a suggested algorithm for de-escalation of therapy considers the evaluation of clinical, endoscopic, radiologic, and biochemical remission and an individual risk assessment, including consequences of the relapse, and patient preference. Although subsequent monitoring is not already established, sequential measurement of CRP or faecal calprotectin every three months is suggested (Chapman et al. 2020).

2. Conclusion

As depicted by this review, several unmet needs in the diagnosis, therapy, and management of IBD remain. In the future, better risk stratification achieved through biomarkers that help stratify patients, predict disease evolution, and tailor therapy may be the solution to overcome the therapeutic ceiling that we are now facing, contributing to the ultimate goal of achieving long-term remission in IBD. Apart from those mentioned in this review, many other unmet needs still prevail and that also need to be addressed.

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CRediT authorship contribution statement

Joana Revés: Conceptualization, Methodology, Investigation, Writing – original draft. **Ryan C. Ungaro:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Joana Torres:** Conceptualization, Methodology, Investigation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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