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REVIEW

Proteomic biomarkers in short bowel syndrome : are we ready to use them in clinical activity?

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ABSTRACT

Introduction: Short bowel syndrome (SBS) is a clinical condition that can affect childhood and adult patients. Biomarker research is expected to be a new frontier in the clinical application, helpful for patients and health-care systems.

Areas covered: SBS is usually a consequence of a massive intestinal resection that leads to an intestinal failure because of the reduction of absorptive surface, bacterial overgrowth, and faster intestinal transit. This new condition requires a multidisciplinary expertise to achieve again digestive autonomy. Parental nutrition (PN) supports nutritional status in SBS patients while the new guidelines on intestinal transplantation confirm its strict indication only for patients at actual risk of death on PN. A PubMed literature review from the 1980s up to date was performed, highlighting proteomic biomarkers and growth factor therapies that have shown so far promising results in SBS patients.

Expert opinion: Apart from a few specific biomarkers and growth factors, the discovery of specific molecular events is currently under investigation of the proteomic analysis and could potentially represent fundamental, future changes in prevention, diagnosis, therapeutic management, and experimental practices in SBS.

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Intestinal resection; short bowel syndrome; intestinal failure; intestinal transplantation; proteomic biomarkers

1. Introduction

Short bowel syndrome (SBS) represents a new frontier in biomarker research. A biomarker is defined as a molecule detected in body fluids or tissues that are associated with a special process (normal or abnormal), a condition or disease[1,2].

In clinical practice, depending on the intended use, biomarkers can be split into *diagnostic, prognostic,* or *predictive*. The first ones are biomarkers whose role concerns the disease detection, the prognostic ones give information on the course of a particular disease (e.g. recurrence, progression, and survival), and the last ones could predict the response to a treatment, which could be subsequently applied on a larger scale[3–6].

The introduction of biomarkers into SBS medical routine practice is expected to become a new field of the research and to represent a new frontier in the clinical application, helpful for patients and health-care systems.

Over the last 20 years, investigators analyzed different proteomic biomarkers leading to the identification of molecules that could help to get a more complete picture of SBS (especially growth factors) and related intestinal adaptation (IA)[7], with the hope to support clinical practice in the near future.

A PubMed literature review from the 1980s up to date was performed on the role of different biomarkers and growth factors that have shown so far promising results in SBS patients. This review offers an overview especially on the new therapeutic approach in SBS patients because the predictive, prognostic, and diagnostic human applications are still mainly at the laboratory stage apart from few clinical exceptions.

2. Short bowel syndrome and management strategies

There are different conditions, varying by age, that can require massive intestinal resection leading to SBS (Table 1). IA in response to the loss of the small intestine is essential to restore enteral autonomy after massive small bowel resection (MSBR) but, when intestinal function is not reestablished, chronic intestinal failure (IF) appears. Virtually all nutrients from the diet are absorbed into blood across by the highly polarized epithelial cell layer forming the small and large intestinal mucosa[8]. IF is the inability to maintain protein-energy, fluid, electrolyte, and/or micronutrient balance[9] developing not only malnutrition, diarrhea, steatorrhea, nutrient deficiencies but also other organ-specific complications such as cholelithiasis, nephrolithiasis, gastric, or liver disease (Table 2).

Wilmore and Dudrick in 1968 demonstrated that parental nutrition (PN) would support nutritional status in SBS[10] and, few years later, the development of home PN made it the standard therapy[11,12].

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Article highlights

- SBS is a critical pathological condition still affected by high morbidity and mortality.
- New diagnostic tools and therapeutic instruments are required to improve outcomes.
- Proteomic research has already come into SBS clinical reality.
- SBS diagnostic proteomic management is still in its developing infancy.
- SBS therapeutic proteomic strategies have indeed obtained relevant clinical results, especially with the use of Teduglutide.

Table 1. Causes of short bowel syndrome varying by age.

Infants	Children	Adults
• Necrotizing enterocolitis • Intestinal atresia • Gastroschisis • Midgut volvulus	• Motility disorders • Postoperative complications • Trauma • Neoplasia	• Postoperative complications • Irradiation • Cancer • Mesenteric vascular disease • Crohn's disease • Trauma • Other benign causes

Table 2. Organ-specific complications related to intestinal failure.

Metabolic	Gastrointestinal	Hepatobiliary	Renal
• Fluid and electrolyte abnormalities • D-Lactic acidosis • Micronutrient deficiency • Malnutrition • Metabolic bone disease • Osteoporosis and osteomalacia	• Gastric hypersecretion • Small bowel bacterial overgrowth • Changes in colonic flora • Diarrhea • Steatorrhea	• Cholelithiasis • Intestinal failure associated liver disease	• Nephrolithiasis • Chronic renal failure

SBS is a consequence of massive intestinal resection that leads to an IF because of the pathophysiological changes related to the reduction of absorptive surface, bacterial overgrowth, and faster intestinal transit.

This condition occurs in approximately 15% of adult patients undergoing intestinal resection; in particular, approximately 75% of these cases are a consequence of MSBR while about 25% derive from multiple sequential resections[13]. The overall 5-year survival is 75% for the patients discharged from the hospital[14] while morbidity and mortality rates depend on the primary disease requiring the resection[13–15].

SBS is a dramatic clinical condition in childhood or adult patients. Furthermore, the medical status can be worsened by complications of IF that, when irreversible, predict a poor prognosis unless a successful intestinal rehabilitation is achieved.

This new condition requires a multidisciplinary expertise to achieve again digestive autonomy: a teamwork is required aiming to add to current therapies also novel approaches (such as manipulation of microbiota or tissue bioengineering)[16]. Prevention of SBS must always be taken into account considering the morbidity and mortality associated with long-term treatment[13–15]. We can recognize: (1) *preoperative strategies* related to patient's primary disease requiring an intestinal resection; (2) *intraoperative* ones that should minimize the extent of enterolysis and resection when this is possible, thanks to surgical techniques such as stricturoplasty, intestinal tapering and lengthening plus second-look procedures; lastly, (3) *postoperative* ones such as strategies to prevent adhesions, avoiding surgical errors, diagnosing intestinal ischemia as soon as possible and approaching the 'frozen abdomen' cautiously[17,18]. In a well-selected population, surgical lengthening procedures, followed by intestinal rehabilitation, could be attempted in order to wean PN off[19].

Thousands of patients are nowadays surviving with SBS[20], but early identification of patients with severe, complicated, and irreversible IF allows to select the ones fit for an intestinal transplant[21,22].

The new guidelines on intestinal transplantation confirm its strict indication only for patients at actual risk of death on PN[23–25]; however, the requirement for lifelong immunosuppression and its associated side effects precludes intestinal transplantation if motivated only by an expectation of improved quality of life[26]. In a long-term view, intestinal transplantation has also demonstrated to be cost-effective compared to PN[24,27,28].

Nevertheless, intestinal transplant itself is not free from complications such as sepsis, multiorgan failure, graft thrombosis, acute and chronic rejection, and post-transplant lymphproliferative disease (PTLD),[29–31] and it should be reserved for a selected patients' population affected by irreversible PN complications.

In pediatric population, the goals of treatment are the same as for adults concerning IA, medical therapeutic options, PN and dietary management, surgical management, and transplantation[32]. One of the most serious complications in children with SBS on long-term PN is intestinal failure-associated liver disease (IFALD). The pathophysiology of IFALD is poorly understood but is likely multifactorial: liver steatosis and fibrosis have been documented to persist for many years after weaning from parenteral nutrition so alterations in intestinal function, along with PN, likely play a role in the pathogenesis of IFALD[33]. Also in children, the main indications for transplantation include severe PN complications, end-stage liver disease (ESLD) secondary to intestinal failure (often requiring a combined liver-intestine transplant), recurrent sepsis, loss of central venous access, ultra-short bowel syndrome, and poor quality of life[34].

3. Intestinal adaptation: diagnostic biomarkers

The molecular mechanisms underlying IA have been investigated in order to find markers able to predict, among SBS patients, the ones will develop IF and the related severity[35].

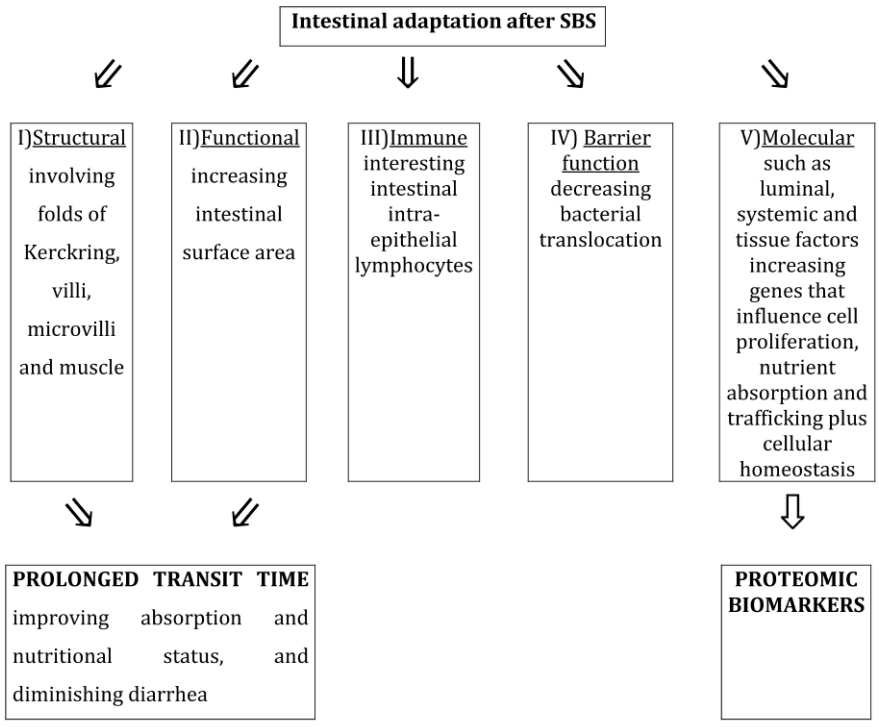

Figure 1. Factors influencing intestinal adaptation.

The proteomic analysis and the discovery of specific molecular events are under investigation, and could represent fundamental changes in prevention, diagnosis, therapeutic management, and experimental practices in SBS.

If the reduction of the absorptive surface area appears, the small intestine has the ability to adapt itself[36] (Figure 1). The IA is a process that occurs generally within the first 2 years after resection inducing a structural response of all intestinal layers (folds of Kerckring, villi, microvilli with subsequent muscle adaptation)[37,38]: as a consequence, the intestinal absorptive capacity improves.

Apart from these *structural* adaptations, other *functional* adjustments occur after intestinal resection, even if this kind of adaptation is less apparent after MSBR: there is a biphasic motor response to varying degrees of distal resection during the first year after the operation[36,39–42].

Controversy remains regarding which residual segment is more beneficial for IA in patients with SBS[43,44]: better a short jejunum or a short ileum? Jejunum and ileum have different roles in digestion, and ileum has probably a greater adaptive potential than the jejunum. A remnant ileum (especially in continuity with the colon) could probably guarantee a faster weaning from PN: the positive role of the colon in digestion among SBS patients has been demonstrated since the 1990s[17].

Summarizing, the first two aspects of IA (structural and functional) lead to prolonged transit time: if diminishing diarrhea, absorption increases and nutritional status improves.

Less studied are the *immune* and *barrier* changes of the intestinal short remnant during IA: the intestinal cell population is formed by more immature and less activated intra-epithelial lymphocytes while bacterial translocation is increased after massive resection[45,46].

Finally, the early *molecular* events have been investigated even if not entirely understood so far: intestinal resection results in increased levels of a variety of gene products[13,47–51] that represent the focus of proteomic analysis because of the great clinical interest as stated above.

Two experimental manuscripts are worthwhile to be quoted in order to qualify the role of diagnostic biomarkers in SBS. Stephens et al.[13] reported the use of a 'proteomic approach' to investigate the intestinal adaptation response in small intestine after MSBR, identifying more than 60 proteins profiling ileal tissue from a porcine model. Among these, three fatty acid binding proteins were chosen for their analysis: L-FABP expression increased in MSBR animals post-surgery, potentially useful as marker of increasing villus surface during IA; FABP-6 protein expression also increased in MSBR animals post-surgery and can act both as a mediator of cell growth and as modulator in bile acid expression; I-FABP was profiled but could not be independently validated in the process of IA. The same proteins were identified thanks to piglet (*Sus scrofa*) models by Jiang et al.[52] as markers of intestinal dysfunction in newborn preterm infants.

More than 90% of children with SBS survive when cared by experienced intestinal rehabilitation programs, and from 60% to 70% undergo IA and achieve full enteral autonomy[53]. Apart from enteral nutrition and absence of IFALD, other primary predictors of IA in children with IF include longer length of remnant small bowel and preservation of the ICV with colon.

The length of remnant small bowel is one of the most important predictors to reach enteral autonomy, especially when expressed as a percentage of small bowel length expected for gestational age[54–57], while the role of ICV plus colon has been known since the '90[58]. Norsa et al.[59] recently

Table 3. Proteomic biomarkers in short bowel syndrome.

Biomarker	Production (cells)	Purpose	Therapeutic use
GH	Pituitary gland	Weight gain, improved energy absorption	Not approved by FDA
GLP-2	L-cells of the distal jejunum, ileum and colon	Improved intestinal absorption, creatinine clearance, fluids/electrolytes absorption and reduction of fecal weight	Teduglutide approved by FDA
GLP-1	L-cells of the distal jejunum, ileum and colon	Inhibit gastric emptying, reduce ostomy output	Not approved by FDA
EGF	Kidney, salivary glands	Pro-absorptive effects improving carbohydrate absorption	Investigational in rat models
Citrulline	Citrulline is synthesized in epithelial cells of the small bowel from amino acids (precursors) Benefits depend on its transformation into arginine	Improves nutritional status and weight gain	Investigational in rat models and clinical trials
IGF-1	Liver, chondroblasts	Induces enterocyte proliferation	Investigational in rat models
KGF	Epithelial cells	Improves gut growth and differentiation	Investigational in rat models
TGF-α	Macrophages, brain cells, keratinocytes	Increases cell proliferation and decreases enterocyte loss via apoptosis	Investigational in rat models
LEP	Adipose tissue	Improves intestinal adaptation, decreasing apoptosis	Investigational in rat models
L-FABP	Cells of the crypts and villi	Marker of increasing villus surface	Not for therapeutic use Investigational in porcine models
FABP-6	Cells of the crypts and villi	Mediator of cell growth, modulator in bile acid expression	Not for therapeutic use Investigational in porcine models
I-FABP	Uncertain expression in cells of the crypts and villi	Increases mitochondrial beta-oxidation and cholesterol uptake → yet to be defined for intestinal adaptation	Not for therapeutic use Investigational in porcine models

EGF: epidermal growth factor; GLP-1: glucagone-like peptide 1; GLP-2: glucagone-like peptide 2; GH: growth hormone; IGF-1: insulin-like growth factor-1; KGF: keratinocyte growth factor; TGF-α: transforming growth factor-alpha; LEP: leptin; FDA: US Food and Drug Administration.

demonstrated the importance of the colon as a salvage organ in pediatric short bowel syndrome (SBS): children with a remnant colon showed absorption rates similar to those without colon thanks to the colonic absorption of lipids and carbohydrates, although the length of their remnant small bowel was significantly shorter. Finally, the influence of the microbiome on enteral tolerance and small bowel bacterial overgrowth should be always considered in pediatric IA[60].

4. Proteomic biomarkers in short bowel syndrome: therapeutic use

After an intestinal resection, crypt and villus enterocytes increase their level of processing a variety of gene products, raising cell proliferation with the goal to enhance absorption, nutrient trafficking, and cellular homeostasis. The interest of the investigators for hormones, proteins, and growth factors is given by the fact that they can promote intestinal expansion; as a consequence, absorptive function increases in order to get 'enteral independence' followed by PN weaning[13,47–51] (Table 3).

Proteomic analysis, performed after resection, has showed so far the involvement of growth factors such as *epidermal growth factor (EGF), glucagone-like peptide 1* (*GLP-1),* and *glucagone-like peptide 2* (*GLP-2)* that regulate gene expression[13,49–61] and manifest a role in the clinical therapeutic field.

The use of growth hormone (GH) with or without glutamine for patients with SBS showed a positive effect on weight gain and energy absorption but these molecules seem to be short-lived, returning to baseline after cessation of therapy. Because of the temporary benefit of this treatment, the use of GH is not recommended in clinical practice and they are not routinely used[62–68].

GLP-2 is a hormone strongly associated with intestinal growth and post-resection IA,[69–73] and many studies have been conducted following the administration subcutaneously of this hormone and/or its synthetic analogue, Teduglutide: the results are encouraging. Intestinal absorption and creatinine clearance improve, achieving the reduction of fecal weight plus the maintenance of fluid and electrolyte's absorption and diminishing the need of total parenteral nutrition[74–76]. In 2019 FDA approved Teduglutide for 1 year and older children with SBS, after the first approval in 2012 for adults[77]. Also in pediatric SBS, the role of Teduglutide is safe and effective with significant reduction of parenteral support and advancements in enteral nutrition re- feeding[78–80].

GLP-1 is another hormone able to inhibit gastric emptying so its loss results in a faster intestinal transit and nutritional depletion. The administration of Exenatide, a GLP-1 receptor agonist, improves bowel frequency in patients with intestinal resection[81,82] but it is still not FDA approved for this use[83]. Another GLP-1 analogue, Liraglutide, has been given subcutaneously once daily in the context of an 8-week, open-label pilot study, reducing ostomy output[84].

Epidermal growth factor (EGF) demonstrated pro-absorptive effects reducing weight loss and improving carbohydrate absorption and intestinal permeability: recombinant EGF is administered enterally in clinical trials, improving absorption and tolerance to enteral feeding, but this agent remains an experimental one[85,86].

Finally, Citrulline promotes body weight gain, preserves muscle trophism, and enhances intestinal adaptation in a model of resected rats through a dose-dependent

mechanism: supplementing diet with Citrulline improves nutritional status after MSBR and jejunum weight is significantly and positively correlated with plasma Citrulline[87].

More experimental are the therapeutic roles of other molecules. Insulin-like growth factor-1 (IGF-1) can promote in rats enterocyte proliferation, which may be beneficial to postoperative conditions such as MSBR including the ICV[88]. Keratinocyte growth factor (KGF) enhances gut growth and differentiation during IA in rat small intestine after MSBR[89]. Transforming growth factor-alpha (TGF-α) increases in a rat model cell proliferation and decreases enterocyte loss via apoptosis[90]. Leptin (LEP) stimulates, during parenteral administration in rats, structural intestinal adaptation, and decreases cell death[91].

5. Expert opinion

Different growth factors have been identified as steps in the adaptation process, and their research for the diagnosis and treatment of SBS has raised considerable interest: however, some issues need to be studied deeply prior to their accepted use as 'proteomic therapy' for SBS patients.

There are study limitations (such as *niche* topic, small samples, unclear parameters, and deficiency of multicenter trials) that still inhibit their application from the animal model to a clinical use[92]: while randomized clinical trials have demonstrated efficiency of GLP-2 analogs, on the other hand during the last 15 years it has been demonstrated that rhGH alone provides poor results unless it is continued for long period while rhEGF was very rarely used in this clinical setting.

In animal models, the comparative effect of GLP-2, GH, and KGF[93] or a 'synergistic effect' of GLP-2 plus EGF[94] has been investigated. Washizawa et al.[93] demonstrated that GLP-2 shows a trophic effect on jejunal growth and also improves mucosal glutathione redox status throughout the bowel after MSBR in rats. Both GH and KGF increase colonic mucosal growth in this model. KGF alone strongly increases gut mucosal goblet cell number and expression of the cytoprotective trefoil peptide TFF3. The different effects reported in this model of SBS suggest that a combined action of these growth factors could maximally improve IA after MSBR but more future studies are needed. Lim et al.[94], on the other side, argued that GLP-2 and EGF are *intestinotrophic*, demonstrating benefit in both animal models and human studies of SBS. Their research shows that over and above known trophic effects, the combination of GLP-2 and EGF synergistically lengthens the bowel in a neonatal piglet model of SBS. Most notable benefits were observed using a piglet SBS model lacking ileum: this condition represents the most frequent remnant anatomy in human neonates, illustrating the potential clinical utility of combined GLP-2 and EGF treatment for human infants with SBS.

On the other side, the role of Citrulline has been investigated in clinical trials discovering another *potential* marker for enterocytes in SBS. Plasma Citrulline is a non-protein amino acid and is considered a biochemical marker of small intestine enterocyte mass in humans. Plasma concentration of Citrulline is about 40 μmol/L and it is produced by enterocytes of the small bowel so can be correlated to residual bowel length in patients with SBS. Citrulline is a marker of acute and chronic intestinal insufficiency because its plasma level reflects the remnant enterocyte mass and absorptive capacity in patients with short bowel[95–97]. Crenn et al.[98] compared the decreased Citrulline plasma level in different conditions with reduced enterocyte mass, independently from nutritional and inflammatory status: it could be used as a *diagnostic* and *prognostic* biomarker in clinical practice for intestinal failure.

Also in pediatric patients, the role of plasma Citrulline helps to monitor residual small bowel adaptation[99] and it can be considered a strong predictor of PN independence in children with SBS: establishing a cutoff plasma Citrulline level can be a *predictive* test for enteral tolerance[100] but also a *prognostic* measure when counseling patients with regards to the likelihood of future PN independence[101].

Norsa et al.[59] emphasized that plasma Citrulline concentrations should be interpreted according to the type of SBS described by the ESPEN anatomical classification system[102]: taking into account the importance of colon preservation, the role of Citrulline represents a reliable marker of small bowel length and enterocyte mass.

Finally, Jeppesen et al.[103] investigated a correlation between plasma Citrulline and Teduglutide: baseline plasma Citrulline showed significant correlations with small bowel length (1) in patients with ≥50% colon remaining/no stoma/colon-in-continuity, and (2) in patients with causes of SBS-IF other than inflammatory bowel disease/vascular disease. Citrulline levels may correlate with parenteral status changes in response to Teduglutide and more research may reveal a deeper relationship with Citrulline levels within the heterogeneous population of patients with SBS-IF. More data can be found looking at U.S. Clinical Trial of reference[104].

Moreover, the potential risks of the use of growth factor therapy need to be evaluated, particularly on a long-term basis. One of the main issues related to the use of these agents is their role as promoters of inappropriate levels of proliferation, which could secondly lead to carcinomatous changes: recent studies have indicated a possible relationship between GH and the pathogenesis of neoplasia[105–107] while EGF has been shown to promote growth of several tumor cell lines[108–111].

It may also be critical to define the correct timing to initiate the growth factor therapy after intestinal resection in order to take the best response to treatment as well as the right duration of administration. More data are required.

Finally, the cost of a treatment with these agents must be compared to weaning PN off: even if growth hormone therapy is expensive (approximately 20.000$ for 1-month supplementation) it seems to be offset by the expense of long-term PN therapy (approximately 100.000 $/year)[112].

Considering all these reported aspects, further studies are indicated before applying these growth factor therapies in the current clinical practice for SBS.

In perspective, restoring early enteral feeding should be the goal of the new therapeutic strategies for SBS patients, increasing IA and eliminating the need of PN or transplantation.

Growth factor therapies, in particular Teduglutide, have shown promising results for IA in SBS patients. Multicenter trials using well-defined outcomes are fundamental to establish (1) the clinical indications for other growth factors, (2) timing and duration of their administration, and (3) evaluate potential risks associated with these therapies.

A 'proteomic therapy' has recently dawned and a significant goal has been achieved in the therapeutic field, especially Teduglutide[113–119] has modified the medical approach to SBS patients, supporting the recovery of intestinal autonomy after MSBR and the related independence from PN. Moreover, the GLP-2 synthetic analogue has improved the results of autologous gastrointestinal surgical reconstruction[120–122], implementing the lengthening procedures on the remnant small bowel, able to support the medical rehabilitation and to avoid transplantation. On the other hand, GLP-1 decreases diarrhea and fecal excretions in SBS patients, but it seems less potent than GLP-2 unless used on a long-term basis. The potential advantages of a combined therapy are still at the laboratory stage: combination of GLP-1 + 2 provides additive effects on intestinal absorption[123] and, as already reported, a similar synergic positive effect on intestinal adaptation in neonatal piglets with SBS has been experimentally obtained by co-administration of GLP-2 and EGF,[124,125] but its clinical application is still far away.

The terrific effort performed worldwide by the proteomic community will certainly produce innovative strategies to diagnose and treat SBS in the next few years, adding new diagnostic means and therapeutic instruments to the armamentarium already in use.

Declaration of interest

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