PSC Support
Helping people affected by Primary Sclerosing Cholangitis
www.pscsupport.org.uk

Clinical need in PSC and clinically meaningful change: What is important to patients?

March 3, 2016

Executive Summary

PSC Support conducted two surveys with over 1,300 respondents to examine Primary Sclerosing Cholangitis (PSC) patients' and caregivers' experiences and attitudes to research, and considered how they could inform targeted clinical outcomes in research.

PSC has far-reaching effects on patients and their families. Living with an incurable, progressive disease with an unpredictable course and symptoms (most common: fatigue, pain and itch), and the added burden of an increased risk of multiple cancers and comorbidities has devastating psychological, social and economic effects. As such, PSC patients are highly motivated to help progress our knowledge of PSC and engage in research efforts.

Patient groups too are eager to work together to drive forward PSC research. Patient groups and individual patients can make valuable contributions to all stages of the research process. **Patient-centred research design** will help recruitment and education, especially where invasive procedures are crucial to the investigation.

Many patients are well informed and willing to learn about and consider participation in future research studies. Patients' priorities for research include the continued study of fundamental science. Even though it may not directly benefit study participants, the progress in our basic understanding of PSC will underpin the future development of targeted therapies and solutions for PSC.

As well as building on existing knowledge of the processes involved in PSC, patients are seeking quality of life improvements, symptom relief and the development of strategies to

improve diagnosis, prognosis and prevention, and to reduce complications/cancers.

Researchers and industry should consider requirements for licensing by regulatory authorities in any trial of a potential therapy for PSC and incorporate patient reported outcome measures (including quality of life) where relevant; we must be prepared to ensure that any successful intervention can made available to patients in the soonest possible time.

The actual experience of PSC is more meaningful to patients than direct physiological measurements, which cannot yet adequately encompass the scope of the condition. Meaningful clinical change therefore has to have a demonstrable, positive effect on the PSC patient experience. As such, this 'quality of life' dimension needs to be captured through patient reported outcomes over time with a view to identifying changes brought about by novel treatments and procedures.

To patients, clinically meaningful change means:

- an improvement in quality of life *that patient can detect*
- the relief of symptoms (e.g. pain, fatigue, itch) *that patient can detect*
- a change in something (e.g. biomarker) directly associated with the disease process that has a convincing ability to:
    - prolong life
    - reduce PSC complications
    - prevent or reduce occurrence of rPSC
    - reduce infection
    - prevent cancer
    - predict (risk of) progression of disease

A concerted, integrated, international approach to PSC research is needed with well-defined research targets and endpoints for therapeutic trials, inclusion criteria and patient-centred trial design. This approach will lead to more effective research and more efficient projects - reducing time-to-results and time-to-revenue. Long-term, realistic goal setting by the PSC research community is fundamental to its success. A great deal of work and challenges lay ahead, but with collaborative effort from all parties, the lives of PSC patients all over the world can be materially improved, and their burden of unmet needs reduced.

Introduction

Primary Sclerosing Cholangitis (PSC) is currently a poorly understood cholestatic liver disease, without an effective prognostic model, or effective treatments. Whilst biochemical markers, imaging techniques and other investigations provide some insight as to the current status of a PSC patient's clinical disease, they do not adequately describe patients' experience of their PSC, that is, how "well" they feel. For example, it is small comfort to a patient if tests results are "good" whilst they continue to experience symptoms that impact their day-to-day life, such as chronic fatigue. As such there are significant unmet needs within the PSC patient community, and therefore an associated high degree of patient willingness to engage with PSC-related research towards identifying treatments and diagnostic/prognostic tools.

Established in 1995, PSC Support is the UK-based PSC patient organisation that provides support and education to those affected by PSC. PSC Support partners with and funds PSC-related research, advocates to research and policy-making organisations on the needs of PSC patients, and promotes PSC awareness in public and medical communities. PSC Support connects with thousands of individuals around the world who are affected by PSC.

Capturing the Patient Experience

This report examines PSC patients' and caregivers' experiences and attitudes, and considers how they can inform targeted clinical outcomes in research. Observations and analysis are made from both anecdotes and results from recent patient surveys made by PSC Support that identify:

- Patients' experience of symptoms and the most challenging aspects of living with PSC.
- Important areas of research for patients.
- Attitudes towards the use of particular invasive procedures in research.
- Attitudes towards treatment goals including survival, quality of life and symptom control.

PSC Support conducted two surveys relating to research and treatments of PSC, which were written by patients for patients and their caregivers/families, and were analysed by patients:

- **PSC Support Research Survey 546 respondents, open 473 days** - Detailed survey for patients and caregivers with questions around unmet needs and research attitudes.
- **PSC Support Treatment Survey 833 respondents, open 18 days** - Focused survey for patients and caregivers to examine attitudes towards treatment goals in research

See Appendix Table A.1 for survey questions.

Over 70% of respondents in both surveys were patients. In the Treatment Survey, we identified respondents who were parents/caregivers of PSC patients under 21 years of age (7.4%).

Acknowledgements

Thanks to the following PSC patient/research organisations for helping to disseminate our Treatment Survey questions and sharing valuable insights into regional unmet needs and important issues for the AASLD/FDA Presentation 3 March 2016.

Organisation	Respondents	Details
PSC Support	520	Treatments Survey
ALBI France	138	Treatments Survey (French translation Q1-5)
PSC Partners Seeking a Cure	130	Treatments Survey (shared survey link)
PSC Kiwi Support and	45	Treatments Survey (shared survey link)
PSC-support (FB primary sclerosing cholangitis & transplant support)		
Total	**833**	

Interpreting Results

While we had an excellent response to our surveys, some selection bias is likely: all respondents were members of one or more PSC patient groups, and each made an active choice to respond to surveys about research.

Our survey results should be taken as an indication of attitudes, experience and opinion only. Open-ended response fields were deliberately used to elicit unbiased answers for some questions. These responses were reviewed and categorised by patients.

Thus our results should be used to better understand the scope and extent of patients' own experiences of symptoms and the most challenging aspects of living with PSC, as well as attitudes towards research and clinically meaningful change.

Unmet Needs

The most difficult part of living with PSC

We asked all respondents to describe the most difficult part of living with PSC. 340 people answered this question, giving 870 concerns, which broadly categorised into the following themes: effect on emotional wellbeing, symptoms, day-to-day activities, social and economic impact (*see Figure 1*).

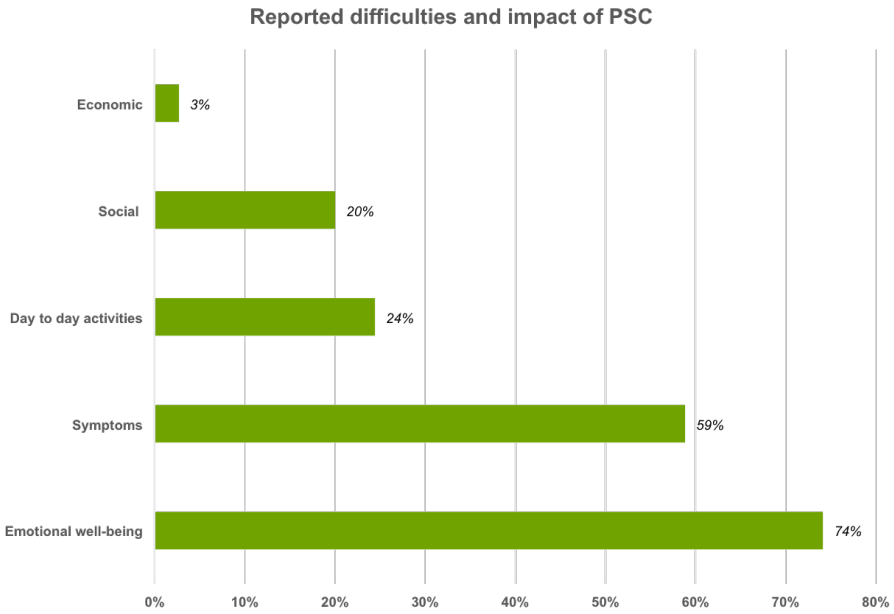

Figure 1. The most difficult part of living with PSC: responses grouped into themes. (n=340)

Emotional Impact

Nearly three-quarters of respondents felt the emotional impact was one of the most difficult aspects of having PSC (see Appendix Table A2.1 for details). The difficulties brought about by the uncertainty associated with PSC are not imagined but are based on the serious reality of PSC.

The answers relating to the emotional impact of PSC were grouped into: uncertainty about the future, helplessness and concern about care and monitoring (see Figure 2).

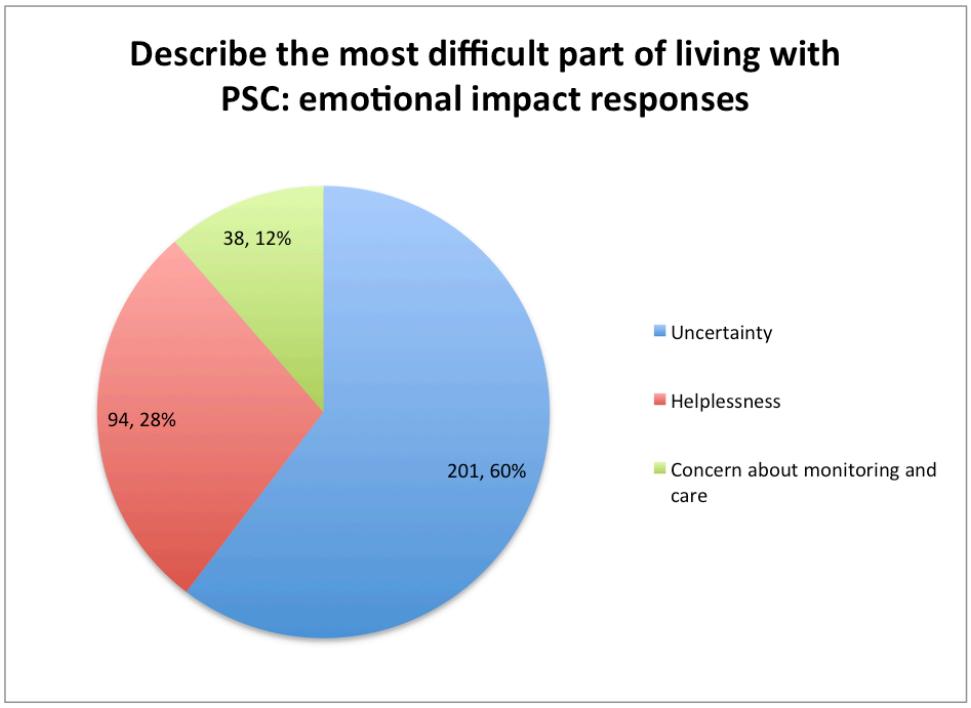

Figure 2. The most difficult part of living with PSC: responses relating to emotional impact.

Uncertainty about the future

60.4% of the emotional impact responses were around **uncertainty about the future**:

Uncertainty about:

1. **Disease progression**

   When a PSC patient is diagnosed, it is not possible to give a prognosis, or any treatment to slow or halt disease progression. This is a cause of considerable concern to patients. Even some asymptomatic patients find it difficult to cope with such a high level of uncertainty and lack of understanding about their own disease progression.

   Implications for research:

   - continue to improve the understanding of the pathogenesis and natural history of PSC
   - develop and establish methods for early

Survey Quotes

"Fear of not being around to see my children grow up."

"I am waiting for a liver transplant, and of course that is stressful. Also concerned that PSC may become malignant before I have transplant. Causes stress for the family."

"Never knowing when I am going to feel well or poorly... pain too at times is hard."

"Knowing it is shortening your life each day"

"The fear of not knowing what the future holds."

"No treatment & uncertainty of what's to come in the future. Also knowing the linked health conditions e.g colon & liver cancer."

identification of different PSC subpopulations and high/low risk groups (risk stratification)
- provide effective, non-invasive prediction and monitoring of disease progression.

2. Transplantation

PSC is the fifth leading cause for liver transplantation in the UK, resulting in 10% of all elective transplants [1]. Our survey found that concerns around transplantation that were threefold: whether disease would **progress to needing a transplant**, whether or not **a suitable organ would become available**, and whether the patient would **become too ill for transplant**.

The supply of donor (liver) organs does not currently meet UK demand, which is increasing, as more and more patients with other liver diseases require transplant. On 31 March 2015, there were 611 patients on the UK active liver transplant list, which represents an 11% increase in the number of patients a year earlier. The number of patients on the liver transplant list has doubled since March 2008[1]. Furthermore, the proposed inclusion of the principle of utility/benefit in organ allocation (under consideration in the UK) is perceived to negatively impact on PSC patients because PSC can sometimes return after transplant (recurrent PSC, rPSC).

The unpredictability of PSC means that some patients decline rapidly and become too ill for a suitable organ to be found and allocated on time. The high level of peer-to peer support in PSC patient communities means that patients are well aware that fellow sufferers can rapidly deteriorate and require transplant, or worse, die. There is a growing concern among the PSC patient community that MELD/UKELD (scoring system to identify patients for transplant) does not adequately reflect the nature and severity of PSC.

Implications for research:
- improve our understanding of the pathogenesis of PSC
- develop and establish methods to interrupt the natural history of PSC to avoid the necessity for liver transplant
- provide effective, non-invasive assessment, prediction and monitoring of disease in patients awaiting liver transplantation

3. Recurrence of PSC after transplant (rPSC)

Our survey found that one of the most difficult aspects of PSC was concern about the return of PSC post-transplant. PSC has been shown to recur in 10% to 27% of PSC patients after transplant[2]. Patients' concerns are well-founded.

Implications for research:

- improve our understanding of the development of rPSC
- provide effective, non-invasive prediction and monitoring of recurrence of disease in post-transplant PSC patients
- develop methods to prevent or interrupt the progression of rPSC

4. Cancer risk

Most patients have PSC and Inflammatory Bowel Disease, and are well aware of the increased risks of cancers; they are reminded of colorectal cancer every year when they undergo their annual colonoscopies. PSC patients are at a higher risk for cholangiocarcinoma, an aggressive cancer that is difficult to diagnose in PSC patients. Early diagnosis is essential for cholangiocarcinoma to be adequately treated because cholangiocarcinoma can be an immediate contraindication for liver transplant in UK transplant centres.

Implications for research:

- understand the risk factors associated with colorectal and cholangiocarcinoma
- provide an **early** diagnostic tool, particularly for cholangiocarcinoma
- provide effective, non-invasive prediction and monitoring of cancer risk with a view to *preventing* cancers

5. Bile duct infections (bacterial cholangitis)

Bile duct infections are causes of hospitalisation and time off work, and for some patients, infection can become resistant to antibiotic therapy. Identification of bile duct infection can be challenging to non-PSC experts, and this presents a problem to

PSC patients for example, when seeking help in hospital emergency departments who do not recognise the presented symptoms as bacterial cholangitis.

Implications for research:

- develop improved methods for identification of bile duct infection
- develop effective therapies for managing bile duct strictures and infection

Helplessness

28.2% of the emotional concerns reported in our survey were around **helplessness**: frustration at having an **'untreatable disease'**, that is not only untreatable, but poorly understood in terms of cause and any kind of prognosis. Questions and comments from our online communities and patient meetings suggest that feelings of helplessness and anxiety are persistent and prevalent, although many patients proactively try to get on with and live their lives as best as they can despite having PSC. In terms of care, there is an unmet need in the provision of psychological support to PSC patients from time of diagnosis.

Implications for research and care:

- provide effective, non-invasive prediction and monitoring of disease progression
- provide psychological support for PSC patients

Survey Quotes

"Watching my son live with this and not knowing how to help."

"Observing PSC friends who have appeared healthy and then experienced a rapid decline and died."

"Watching him in pain and not being able to help. Family life falling apart as we are unable to plan.....he is tired all the time and we worry about finances."

"Seeing my dad suffer and not being able to find a cure for it…"

"Watching someone you love having their energy and well being stolen, their choices reduced whilst being unsure of the of my family's future without the power to help change the course of this unpredictable, treacherous disease."

Perceived inadequate clinical care and monitoring/burden of hospitalisation

11.4% of the emotional concerns reported were about perceived inadequate clinical care or monitoring, and the burden of hospitalisation.

PSC is a rare disease and, understandably, clinicians with an interest in and experience of PSC are not accessible locally to every patient. Some of the concerns expressed relate to the **lack of access to PSC experts** and/or **inconsistency in monitoring and care** between different care providers. However, other concerns over care related to the fact that the **monitoring of PSC itself currently provides little reassurance to the patient**. For example, abnormal LFT (liver function test) results often produce more questions than they answer given that there are few effective therapeutic options currently available.

Invasive procedures, which increase a risk of much-feared infection and complications, are also a source of concern. PSC Support frequently hears from patients, whose LFT results are within the normal range, struggling because they feel unwell or are in uncontrollable pain.

Patients who have concerns about their current health status (for example, suspicion of bile duct infection) often turn to patient support group communities for help because they do not have easy **communication channels with their care providers**. As a result there can be an unnecessary lag between the point that the patient feels unwell to the point that they are able to engage with their hepatologist and receive treatment. Care providers should **leverage virtual communication technologies** to bridge this care gap. With planning, this would provide an opportunity to provide prompt clinical management of patient reported symptoms, as well as enhancing research opportunities for patients.

Survey Quotes

"PSC has required many tests, procedures and interviews related to being accepted as a liver transplant candidate"

"I would like clear answers to my questions regarding the state of my liver Some of the worry in my mind could be reduced if I felt more confident in my consultant at the local hospital."

"Getting people to understand is difficult as they go along the lines of "you don't look ill"

"Dealing with lack of knowledge from medical professionals and inconsistencies in care and monitoring."

"Lack of understanding on friends an family but also doctors who we have to see in local hospitals"

"Trying to lead a normal life while suffering from symptoms that most people don't understand or can't relate to."

"Unpredictable cholangitis attacks causing unplanned hospital visits. The difficulty of identifying the symptoms of an attack."

"Dealing with a great deal of pain, constant infections or blocked stents, despite being on antibiotics all of the time."

The **lack of psychological support** for patients diagnosed with PSC is another common concern and a real issue for some patients. Even when a PSC patient is asymptomatic, they still carry a huge emotional burden of this 'untreatable' disease.

Implications for research and clinical care:

- provide psychological support for PSC patients
- develop national and international networks of centres of excellence for care and research, such as the forthcoming European Reference Networks
- standardise global clinical care/monitoring guidelines
- develop virtual PSC clinics and portals so that location is no longer a barrier for access to expertise and research opportunities

PSC is a disease that has no known cause, no curative treatment, unsatisfactory monitoring and a great weight of uncertainty around progression and cancer. It is no surprise that most respondents expressed some emotional element was the most difficult part of living with PSC.

Social Impact

20% of respondents talked of the social impact of PSC when considering the most difficult aspect of PSC (see Appendix Table A2.2). This a lower proportion than PSC Support anticipated, because day-in day-out, comments are made to our online communities about the effects of **social isolation** and the **guilt** expressed about not being able to adequately care for one's family.

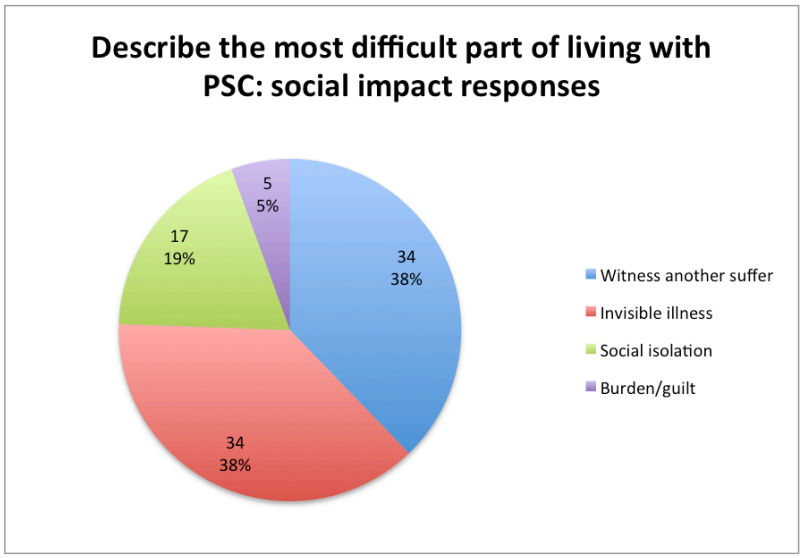

Figure 3. The most difficult part of living with PSC: responses relating to social impact.

The concerns expressed were mostly (38%) around a **lack of understanding** from others, or rather, the effects of having a mostly **invisible** illness, and the same proportion noted how difficult it was to stand by and watch someone else suffer or die (see Figure 3). 19% of the concerns were around social isolation and 6% were around **being a burden** to others.

Implications for research and care:

- include quality of life measures in research where scientifically justified.
- provide psychological support for PSC patients

Survey Quotes

"The debilitating fatigue I experienced along with several other symptoms such as HE, itching etc meant that I was unable to lead a 'normal life' I was housebound most of the time, I had to give up work and I was unable to socialise with my friends and family. This was extremely difficult to deal with as someone who is in their early 20s. I often felt isolated and like my life was on hold until I got my transplant."

"Watching him in pain and not being able to help. Family life falling apart as we are unable to plan.....he is tired all the time and we worry about finances."

"Juggling my life around PSC. I feel like a burden."

"Pain: can prevent me from being able to do the things 22yr olds do and getting people to understand is difficult as they go along the lines of 'you don't look ill'"

Symptoms

In our Research Survey, when asked to indicate the **symptoms they had experienced *in the previous four weeks,*** the most common symptoms indicated by patients were fatigue, pain and itching (78%, 54% and 51% of respondents respectively) (see Figure 4). 317 patients answered this question.

5% of respondents indicated that they had had **no symptoms** in the previous four-week period.

More than one third (32%) reported that they had **felt depressed**. Although this is a self-reported symptom, it demonstrates that PSC comes with a heavy emotional burden for some patients.

When constructing this question, we underestimated the scope of symptoms experienced (see Appendix 1 Table A1 PSC Support Research Survey Question 3). The *'Other (please*

specify)' answer to this question (see Appendix Table A2.4) revealed many more symptoms important enough for patients to mention, ranging from early menopause, bloating and weight loss, nausea, specific joint pain, bleeding gums, to sleep problems not associated with itch. Some of these additional symptoms related to the other diseases so many PSC patients also have (eg IBD), showing the complexity that PSC presents.

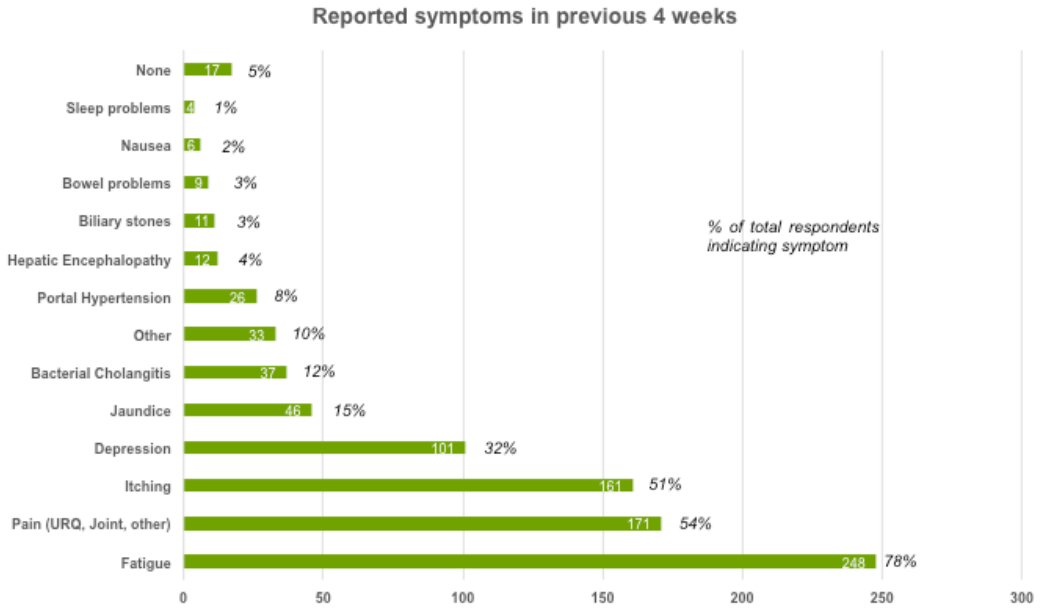

Figure 4. Tick the symptoms you have experienced in the last four weeks.

In our Treatment Survey, we asked what was **the most difficult aspect of PSC**, and again, **fatigue, itch and pain** were the most commonly cited symptoms (see Appendix Table A2.3 for details and Figure 5).

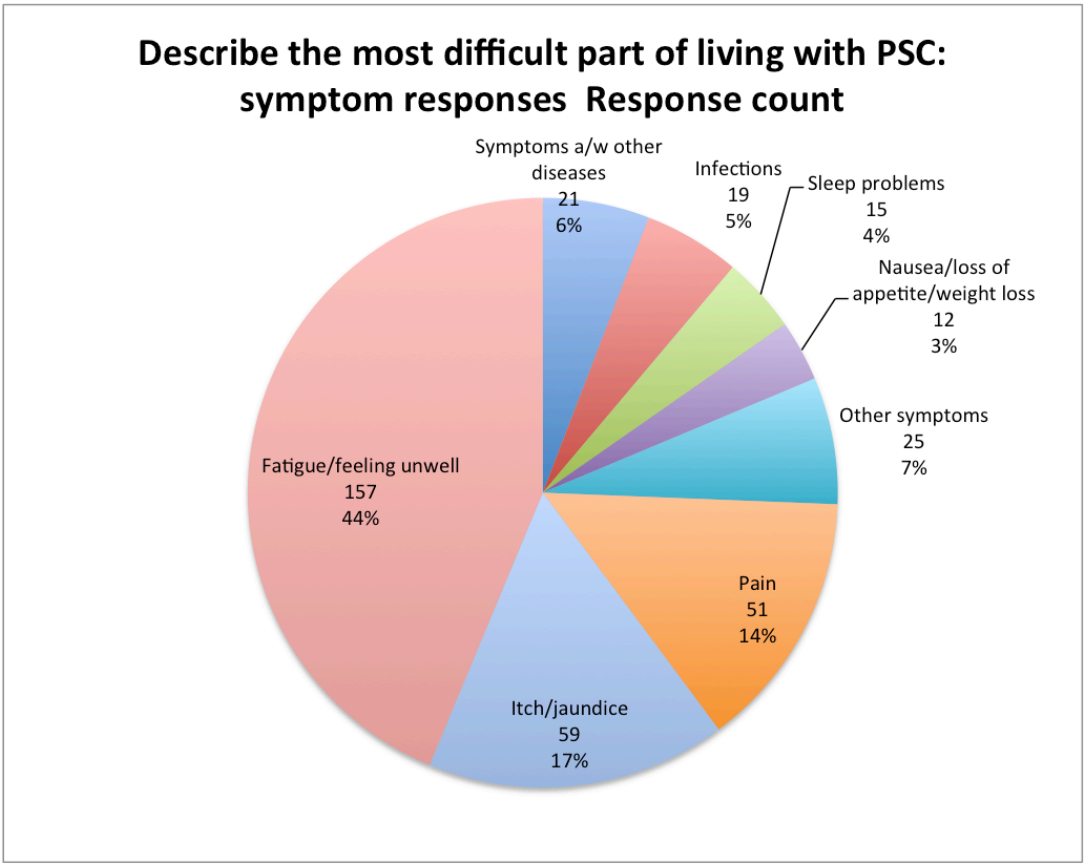

Figure 5. The most difficult part of living with PSC: responses relating to symptoms.

Fatigue

Fatigue is sometimes ignored or not acknowledged by non-expert clinicians when no other underlying cause is identified. It is likely that 'fatigue' in PSC patients takes different forms, ranging from feeling generally unwell (perhaps from constantly fighting off low level bile duct infection) to debilitating fatigue. It is even sometimes seen in otherwise asymptomatic PSC patients. Many patients report finding it difficult to think clearly when suffering from fatigue.

Implications for research and care:

- define, evaluate and measure fatigue and cognitive function in PSC patients
- develop effective therapies for fatigue management
- use good quality patient reported outcome measures to measure pruritus and quality of life
- proactively enquire about fatigue in clinical care

Pain

PSC patients are regularly told by attending clinicians that it is not possible to feel pain in the liver. Discussions in our online communities tell a different story, with patients **struggling with inadequate pain relief.** Patients can sometimes be left in severe uncontrollable pain with general practitioners unable or unprepared to manage it.

Implications for research and care:

- evaluate and measure pain in PSC patients
- develop effective pain management for patients
- use good quality patient reported outcome measures to measure pain and quality of life
- proactively enquire about pain in clinical care

Pruritus

Pruritus is a persistent and major problem for some patients, especially in cases where it does not respond adequately to available medications, or where patients are simply not offered alternatives when the first line of therapy does not work, or where the patient finds existing pruritus therapies difficult to tolerate. Pruritus can be an underlying cause of sleep problems and associated fatigue, as well as a having major impact on quality of life. Further research is needed to better understand cholestatic itch and find more effective ways to ameliorate it.

Implications for research:

- improve understanding of cholestatic itch
- develop improved pruritus therapies
- use good quality patient reported outcome measures to measure pruritus and quality of life

Survey Quotes

"Feeling tired all the time"

"Constant fatigue, head constantly feeling like full of cotton wool..."

"The pain and exhaustion. I am being constantly told there is no pain with this disease!"

"Pain and fatigue can be debilitating sometimes. Especially being a working mother."

"I have had the PSC return after transplant. There are more symptoms to deal with than there was before. I seem more fatigued this time round."

"Prior to transplant life was very difficult, I itched beyond control, my quality of life was just an existence I couldn't wear clothing for more than a couple of hours without wanting to tear my skin from my bones, each inch of my body itched.."

"Having to watch your child in pain and scratching herself till she bleeds."

"Also I wake up at night itching. I had to cut my hours at work, because of getting so tired."

Impact on Day-to-Day Activities

A quarter of respondents answering this question reported that one of the most difficult aspects of PSC was the impact it had on the ability to take part in activities - impacting on family life, school and college, work life and retirement. Many cited fatigue as the cause of the inability to perform activities (see Appendix Table A2.5 for details).

Implications for research:

- include quality of life measures in research where scientifically justified

Survey Quotes

"Unable to fulfill my dreams in retirement."

"I have also lost confidence that I could do a full time job. I'm currently self employed and can fit my work around when I'm feeling well but I would actually like to get a job."

"Extreme fatigue stops me from keeping a steady job"

"I had to cut my hours at work, because of getting so tired."

"The tiredness, depression & itching affects me most, I am retired so on bad days I don't do anything but try and cope with the illness, if I was still working I wouldn't be able to cope."

Economic Impact

Although only 3% of respondents mentioned the financial impact of having PSC as the *most difficult* part of living with PSC, it is a major problem for many PSCers and warrants further research to evaluate its true impact. Many of the answers expressed worry about the fact that they could no longer work full time or not work at all (see Appendix Table A2.6 for details).

Survey Quotes

"...a loss of income, causing financial stress."

"The fatigue issues mean I no longer work night shifts. This has had a major impact at work, and on income levels."

"Itching is my worst symptom. It is alleviated by sunbeds combined with Sertraline, but the fortnightly 40mile round trips for the sunbeds is time consuming and costly - but better than not going."

"Fatigued a lot, had to give up work so now struggle on benefits (have own house and mortgage)."

Patients with PSC and fatigue struggle to achieve full time working hours and find themselves reducing their hours or even unable to work, yet still needing to provide for their families. Often with lower financial income, they are expected to pay (UK) for their multiple medicine prescriptions, and (in other countries) are also required to pay for healthcare. Time needs to be taken off work for hospital appointments, and childcare arranged and paid for. Accessing financial products (such as mortgage, life, health and travel insurance) is difficult for PSC patients; many providers increase premiums, apply additional terms or even refuse to provide cover.

Implications for research:

- include quality of life measures in research where scientifically justified

- undertake health economics research for PSC
- develop and establish methods for early identification/prediction of risk for different PSC subpopulations and high/low risk groups (risk stratification) - to allow differentiation in financial products

Quality of Life

Our survey shows that there are quality of life issues for PSC patients and it is important to develop treatments for PSC that improve quality of life. Equally, it is important that quality of life is not made worse by novel therapies for PSC. However, **no validated health-related quality of life measure specifically for PSC exists yet there is a critical need for such a tool**[3].

PSC Support is developing a PSC-specific quality of life instrument in UK patients and will proceed to validate this internationally. The initial funding for this project has been provided by the British Liver Trust and will be used to fund a PhD student to undertake the work. The principal investigator is Dr Douglas Thorburn and the project will be supported by experienced qualitative researchers from the UCL Marie Curie Palliative Care Research Department. The project is expected to be complete in 2018/9 with the international validation completed by 2020/1.The steering committee includes Martine Walmsley (patient, PSC Support), Andrew Langford (patient representative, British Liver Trust), Dr Thorburn (Royal Free Hospital, London UK) and Dr Hirschfield (Queen Elizabeth Hospital, Birmingham UK).

This tool will be a key measure of the impairment of quality of life in patients with PSC and will be suitable for multicentre international clinical trials, to evaluate the responses to new treatments for PSC.

Important areas of research for patients

Patients and their families provided 530 questions when asked to state "unanswered questions" regarding PSC research (see Appendix Table A2.7a to A2.7e for summary of 'unanswered' questions asked).

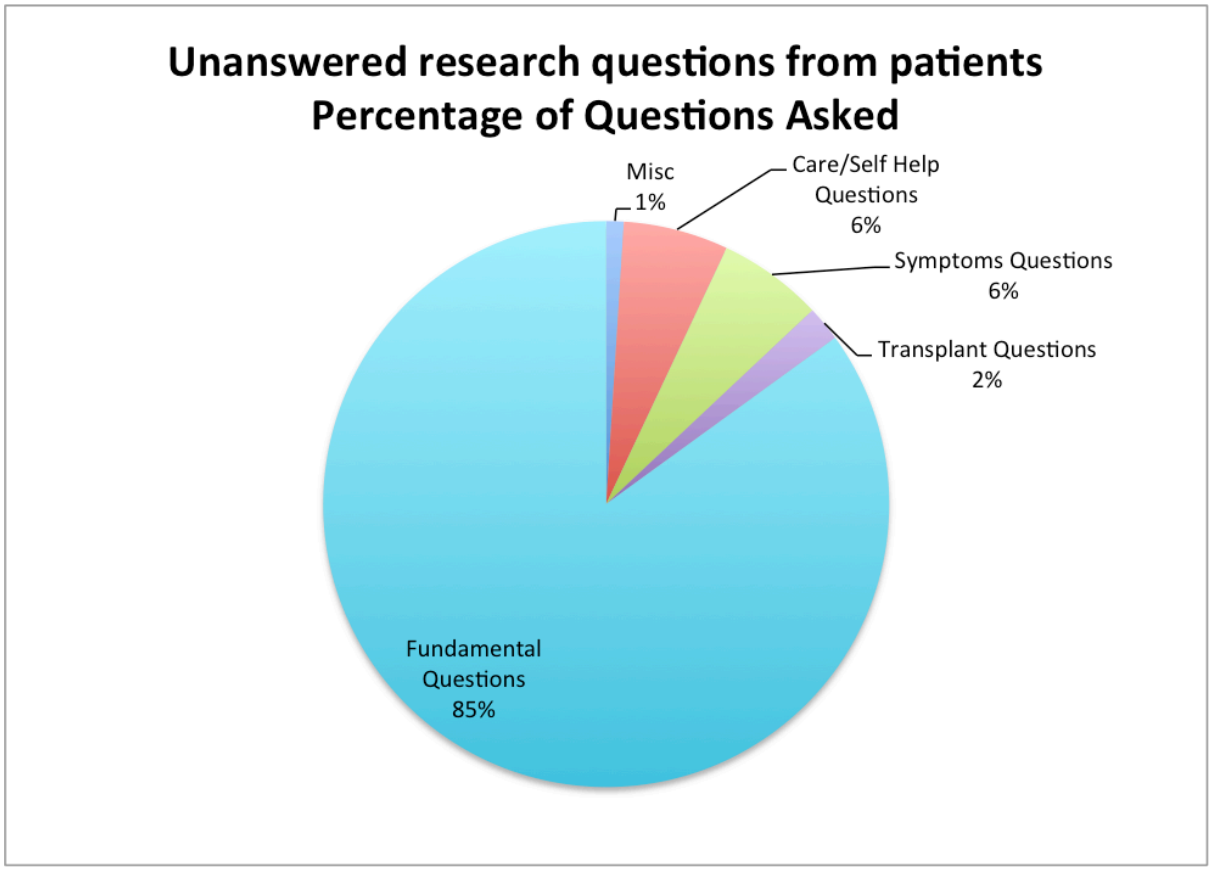

Figure 6. What "unanswered question" would you like answering about PSC? Types of questions.

By far the most common responses (85%) were **fundamental, sense-making questions** about PSC (see Figure 6). Interestingly, many questions revolved around knowing the 'cause' of PSC. Questions enquiring about the mechanism of action/cause and genetics of PSC can be attributed to:

i) patients' awareness that a greater depth of understanding is needed if we are to find treatments for PSC

ii) patients' understanding that there are already several proposed mechanisms for the pathogenesis of PSC under investigation

iii) a fear of children or family members having PSC.

There were also questions seeking to understand:

- interventions that could change the natural history of PSC/rPSC (halt progress, repair damage or cure)
- prevention of PSC/rPSC
- early and definitive diagnosis of PSC/rPSC/cancers
- prognosis
- identification of subgroups of PSC including high/low risk groups of patients.

Patients encourage investigations to **identify subpopulations of PSC**, recognising that the outcomes of future trials may be dependent on having 'similar' patients in trial cohorts, based on subgroups such as high/low risk, age, severity of fibrosis, colitis status etc.

In particular, some questions focused on the **detection/prevention of cancers**. Detection of cholangiocarcinoma ***early enough to allow for effective treatment*** is of prime importance for PSC patients.

Other fundamental research questions included investigating the **links between PSC and autoimmune diseases**.

There were relatively few questions addressing **symptoms** (6%) but we can assume that the fundamental questions themselves encompass symptoms and quality of life issues.

With no licensed treatment to cure PSC, understandably, some questions asked about ways **patients could improve their situation themselves**: specific diet, lifestyle choices, clearer care pathways, clinician education and awareness and improved, non-invasive monitoring.

From the range and type of questions asked, undoubtedly many PSC patients are informed about their disease and understand there is no current treatment available to **prevent, slow or halt progression**.

Patients are **realistic** too. We understand that there will be **no miracle treatment or cure overnight;** this is a long-term goal. We understand that a single treatment won't address all our challenges. However we welcome **improvements to quality of life** and steps towards treatments such as **effective non-invasive diagnostic and monitoring tools and cancer detection/ prevention.**

PSC patients want to work with researchers to help find treatments, if not for themselves, for other patients. Patients realise and accept that fundamental research is required to improve our understanding of PSC and **identify useful biomarkers**, which may not provide immediate direct benefits to participants.

Attitudes towards the use of particular invasive procedures in research

We asked patients what clinical procedures they had undergone and which they would be prepared to undergo for research. 317 patients answered these questions (see Appendix Table A2.8 and A2.9)

PSC patients in general are interested in and want to be involved in research (see Figure 9), with most being prepared to take MRI scans (90%), CT scans (85%), bone density scans (87%), fibroscans (72%), ultrasounds (94%), and provide blood (95%), saliva (92%), stool (84%) and urine (94%) samples (see Figure 7)

Patients' attitudes are positive about invasive procedures for research, with around half prepared to undergo a colonoscopy (58%), biopsy (52%), gastroscopy (52%) or ERCP (55%).

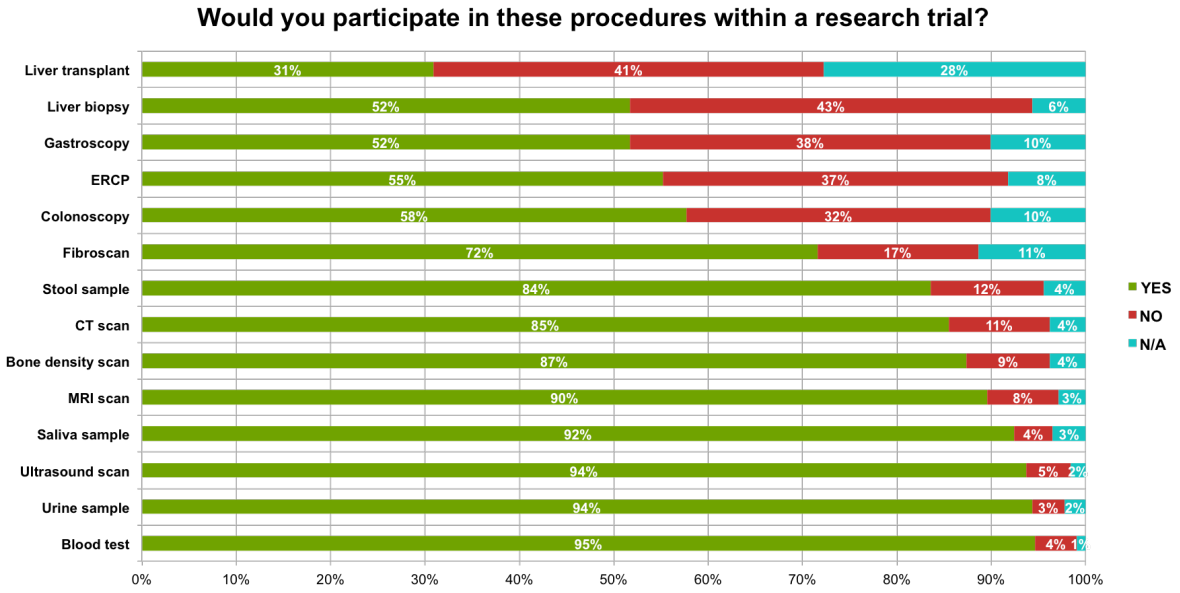

Figure 7. Responses to question: Assuming that you were happy with all other aspects of the study, would you participate in a research trial requiring...

Biopsies

PSC Support is often asked about patients' willingness to participate in research studies that require biopsies. Because of the discomfort and risks associated with biopsy, and the surprisingly positive attitudes revealed in the PSC Support Research Survey (52% would have a biopsy), we asked the same question to patients in isolation in our shorter PSC Support Treatments Survey. 618 patients answered this question. This time, we found an even higher proportion (66%) was prepared to undergo biopsy for research (see Figure 8).

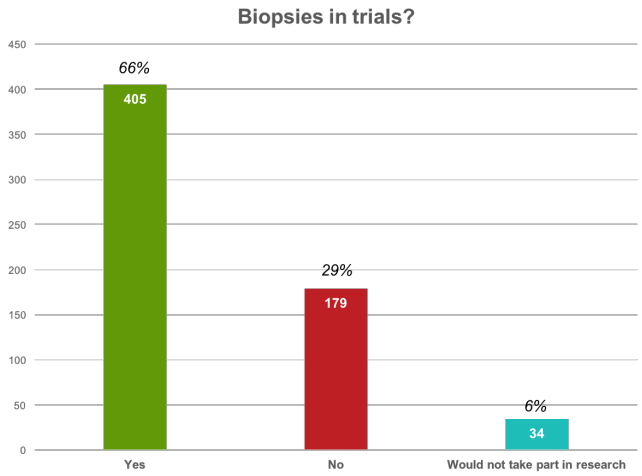

Figure 8: PSC patients only: If you were taking part in a research trial, would you be prepared to have one or more biopsies? (PSC Support Treatments Survey)

This figure held true even for patients who had previously had a biopsy, and was even higher for PSC Support respondents only (see Table 2). It is hard to explain this increase. One possibility is that there are cultural differences in attitudes to biopsies. PSC Support respondents were likely to have been predominantly British. ALBI respondents were likely to be predominantly French.

It is possible that by virtue of the fact that they were filling in a research survey, respondents were already interested in research, and so there was some selection bias. Examination of the open comments associated with this question revealed that **patients are well aware of**

the risks and complications of biopsies and did not like them, often finding them distressing and painful.

Responses indicated that there was concerning variability in the way in which biopsies are being administered to patients. Many patients quite rightly stated that they would want more information in order to make their decision in real life.

PSC patients are informed and alert to the risks and benefits of procedures, and the need for PSC research. Patients want to help research and are aware of the costs to them of having biopsies. It should not be concluded that PSC patients want biopsies as part of their routine care; they don't. **PSC patients are engaged and willing to take part in research but not at any cost.**

We should be crystal clear about this: **no one likes a biopsy or takes one lightly**.

Patients understand that there may be a role for histological sampling in research studies. When this is the case, **patient recruitment and retention in the studies will be paramount**. Patients and patient groups should be engaged in the whole research process from designing the study right through to involvement in preparing licensing evidence in the case of an effective compound. **Patient –centred research** can shorten time-to-result and time-to-revenue (for investors) by supporting recruitment, education, design and focusing on what is important to patients.

Survey Quotes

"It was one of the most horrible things that I have had done to me."

"I would take part but only if it won't hurt like the last time I had a biopsy done."

"I answered "no", but if the clinical trial sounded very promising, I might undergo a biopsy."

"Biopsies hurt, but PSC is sucking the life out of me."

"It was one of the most painful experiences of my life. Unless absolutely necessary I would not like to repeat it."

Table 2. If you were taking part in a research trial, would you be prepared to have one or more biopsies? (PSC Support survey results only)

Previous Biopsy?	Would have a biopsy for research (%)	Would not have a biopsy for research (%)	Would not take part in research
Yes (n=352)	250 (71%)	88 (25%)	14 (4%)
No (n=137)	97 (71%)	33 (24%)	7 (5%)
Total (n=489)	331 (71%)	112 (25%)	21(4%)

Research implications:

- involve and engage patients in the whole research process including the study design and protocol
- investigate cohort willingness for biopsy when designing the research
- biopsies should only be part of the study protocol if it is absolutely necessary (or when they are part of existing clinical care), when there is no other way of obtaining the desired information
- participants undergoing biopsies should be administered adequate sedation and such procedures be conducted by experienced practitioners only
- there should be a convincing and important reason for the use of biopsies in research design.
- Provide comprehensive lay information about the trial including why the invasive procedure is important.
- Engage patient groups to support patient education

Attitudes Towards Treatment Goals

Treatment priorities

We asked respondents to rank what was most important about a PSC treatment. Not surprisingly, most people (80%) choose prolonging life and controlling symptoms as their priorities (see Figure 9) but the range of answers indicate that actually the side effects of treatments and administration were more important to some patients. It is likely that attitudes to this question are very much affected by disease severity and/or complications.

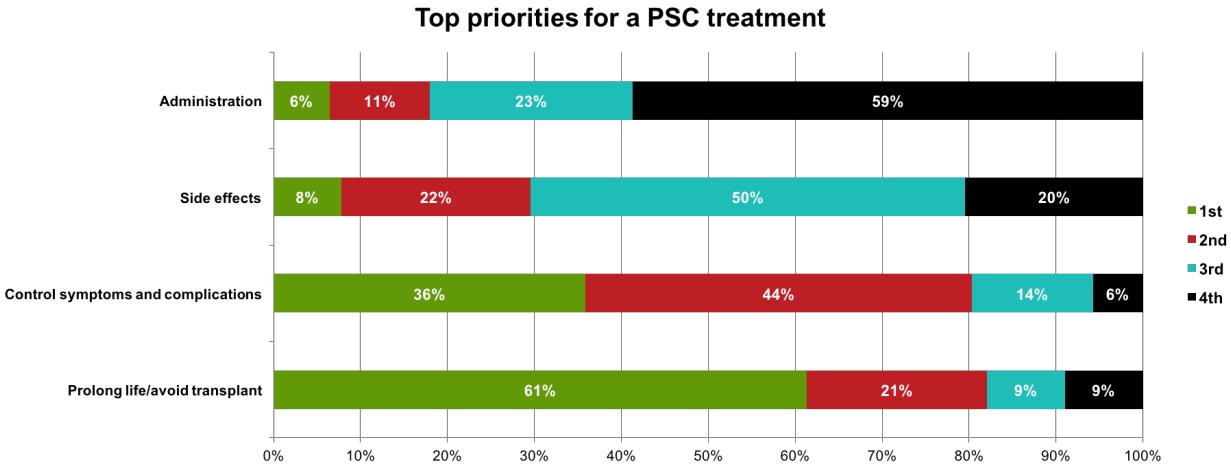

Figure 9 Rank what is most important to you about a PSC treatment: (1= most important; 4=least important)

The results of our questions on unmet needs concerns around cancer, death or liver transplant and some symptoms and complications (including recurrent infection) were major difficulties for people affected by PSC. We wanted to know if one of these areas was of greater concern than the others.

We asked, *'Right now, if you had to allocate 100 points among each of these treatment areas, how many points would you give each?'* The results showed a spread of allocations (see Figure 10 and Appendix Table A2.10). Avoiding death or transplant came out ahead but the pattern of responses was widespread. Some respondents allocated the majority of their points prolonging life or to the control of symptoms and complications.

For a disease with no curative options and an increased risk of cancers compared to the general population, this was a difficult question to answer, and not surprisingly, there was no clear individual concern a long way ahead of any other. Most points allocations were around 33 suggesting a generally equal weight of importance to each factor. Some respondents allocated the majority of points to either avoidance of death or transplant, or to control of symptoms.

When faced with a disease that has an increased risk of cancer as well as risks of uncontrollable symptoms and complications, as well as a risk liver failure (death or transplant), ranking importance to each factor is nigh on impossible.

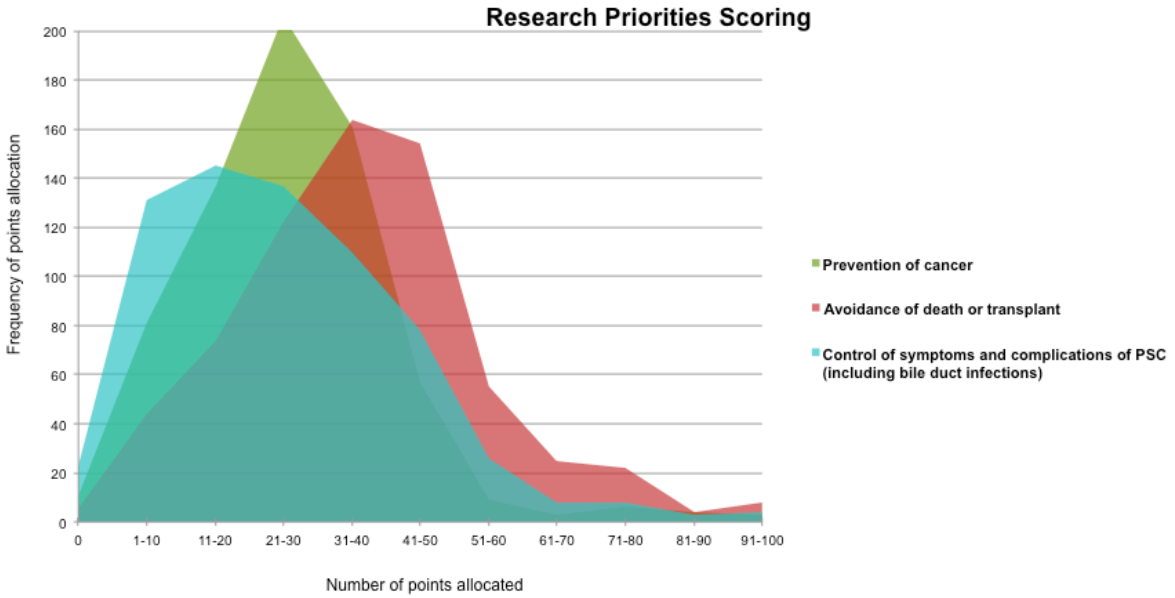

Figure 10 Right now, if you had to allocate 100 points among each of these treatment areas, how many points would you give each?

PSC patients often read or hear about research studies that use Alkaline Phosphatase (ALP) as a prognostic marker. However, a change in ALP is not necessarily meaningful to patients, since ALP levels rise and fall in routine tests without a clear association with how the patient feels. We asked patients another difficult question: how confident they felt that changes in ALP would prolong life, improve quality of life, control symptoms, decrease the risk of transplant, and reduce the frequency of bile duct infections.

Most patients were 'Not sure', citing the need for more details in order (in open-ended response option) to make an informed decision (see Figure 11). This is important to note because if participants are to be successfully recruited into research studies, they need to be provided with adequate information. Our PSC patient communities are hungry for information on all aspects of research.

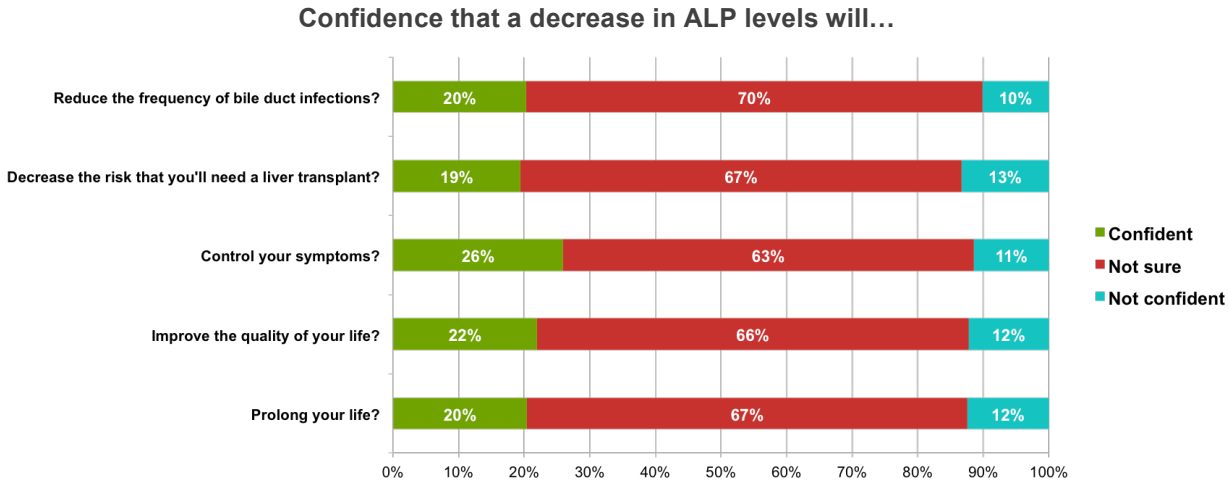

Figure 11 Research was published this month concluding that a decrease in ALP levels (a component of regular blood tests for PSC patients) to within the normal range was associated with improved long-term survival and decreased risk of needing a liver transplant for PSC patients. *The normal range refers to expected levels in a healthy person. It is possible that some researchers may wish to use ALP levels to determine whether or not a PSC treatment is effective. How confident do you feel that a drug that improves ALP will...*

Clinically Meaningful Change for Patients

Based on the answers to our surveys, we know that there are unmet needs over a range of areas for PSC patients. Research should consider addressing areas to improve quality of life for patients, to relieve symptoms and to develop strategies/biomarkers to improve diagnosis, prognosis, prevention and to reduce complications/cancers.

The actual experience of PSC is more meaningful to patients than direct physiological measurements, which cannot yet adequately encompass the scope of the condition. Meaningful clinical change therefore has to have a demonstrable, positive effect on the PSC patient experience. As such, this 'quality of life' dimension needs to be captured (when

appropriate) through patient reported outcomes over time with a view to identifying changes brought about by novel treatments and procedures.

There is an urgent need to identify surrogate endpoints in PSC yet it is difficult for a number of reasons, not least because PSC is rare, likely to be composed of subtypes, and the fact that it is not only a complex condition involving biliary fibrosis, cirrhosis and cholangiocarcinoma but also frequently associated with Inflammatory Bowel Disease. Direct endpoints, such as death, liver transplant, cholangiocarcinoma or advanced liver disease complications are not feasible because they would require long-term studies over many years.

We hope that new surrogate markers can be evaluated in trials alongside existing ones. In particular, patients are interested in a range of markers being developed such as new imaging modalities (transient elastography or new magnetic resonance (MR) techniques such as MR elastography and multiparametric MR scanning) or serum markers of fibrosis.

To patients, clinically meaningful change means:

- an improvement in quality of life *that patient can detect*
- the relief of symptom (e.g. pain, fatigue, itch) *that patient can detect*
- a change in something (e.g. biomarker) directly associated with the disease process that has a convincing ability to:
    - prolong life
    - reduce PSC complications
    - prevent or reduce occurrence of rPSC
    - reduce infection
    - prevent cancer
    - predict (risk of) progression of disease

Conclusion

Primary Sclerosing Cholangitis has far-reaching effects on PSC patients and their families. Living with an incurable, progressive disease with an unpredictable course and symptoms, and the added burden of an increased risk of multiple cancers and comorbidities has

devastating psychological, social and economic effects. The most common symptoms experienced are fatigue, pain and itch.

As such, PSC patients are highly motivated to help progress our knowledge of PSC. They are well informed and willing to learn about and consider participation in future research studies. Patients' priorities for research include the study of fundamental science, even though it may not directly and immediately benefit research study participants but will underpin the development of targeted therapies and solutions for PSC.

Patient groups, too, are eager to work together to drive forward PSC research. Patient groups and individual patients can make valuable contributions at all stages of the research process to inform design, recruitment, education and dissemination of information.

A concerted, integrated, international approach to PSC research is needed, building on the excellent work of the International PSC Study Group, with well-defined research targets and endpoints for therapeutic trials, and patient-centred trial design. This approach will lead to more effective research and more efficient projects - reducing time-to-results and time-to-revenue. Long-term, realistic goal setting by the whole PSC research community is fundamental to its success.

A great deal of work and challenges lay ahead, but with collaborative effort from all parties, the lives of PSC patients all over the world can be materially improved, and their burden of unmet needs reduced.

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Appendices

Appendix 1

Table A1. Survey Questions

PSC Support Research Survey **(07 Oct 2014 to 22 January 2016, 473 days) - 546 responses**	**PSC Support Treatments Survey** **(08 Feb to 25 Feb 2016, 18 days) - 833 responses**
*1. Where do you live? (State the country in which you normally live) *2. Are you a... ● PSC patient or have had a liver transplant for PSC ● Parent/partner of someone with PSC ● Friend/family of someone with PSC ● Medical professional ● Other (please specify) 3. PSC patients only: Tick the symptoms you have experienced in the past 4 weeks: ● Fatigue ● Upper right quadrant pain ● Itching ● Portal Hypertension ● Hepatic Encephalopathy ● Depression ● Biliary stones ● Jaundice ● Bacterial Cholangitis ● Other (please specify) 4. PSC patients only: Tick the procedures and tests you have ever had: ● Blood test ● ERCP ● CT scan ● Ultrasound scan ● Bone density scan ● Liver transplant ● Liver biopsy ● Stool sample ● Gastroscopy ● Urine sample	1. Please indicate your interest in PSC: ● I am a PSC patient and I have not had a liver transplant ● I am/was a PSC patient and I have had a liver transplant for PSC ● I am the friend/family of an adult PSC patient (aged 21 or over) ● I am a family member of a PSC patient under the age of 21 ● Other (please specify) Some research studies might require you to have a biopsy, for example, trials using molecular pathology (a high-tech approach studying biological processes) to look at the molecular characteristics of PSC. We would like to understand your appetite for having biopsies in trials. *2. PSC patients only: have you ever had a liver biopsy? ● Yes ● No *3. PSC patients only: If you were taking part in a research trial, would you be prepared to have one or more biopsies? ● Yes ● No ● n/a - I would not take part in a future trial Please let us know if you have any additional comments about biopsies. We are interested in what is most important to you in research trials. Your answers to these questions are important and will help us give a balanced and representative picture of your views.

- MRI scan
- Colonoscopy
- Fibroscan
- Saliva sample
- Other (please specify)

Research trials often require the patient to undergo certain procedures.

*5. PSC patients only: Assuming that you were happy with all other aspects of the study, would you participate in a research trial requiring: (No, Yes, N/A)

- Liver transplant
- Fibroscan
- Stool sample
- Urine sample
- Blood test
- Liver biopsy
- Saliva sample
- CT scan
- MRI scan
- Gastroscopy
- Bone density scan
- ERCP
- Ultrasound scan
- Colonoscopy

Life with PSC can be difficult, but everybody is different. We want to know how PSC affects you and your family.

6. Describe the most difficult part of living with PSC.

7. How would an effective treatment for PSC affect your life?

8. Why should researchers focus on PSC?

As well as listening to patients about the design of their studies, researchers want our views on the direction of their research, that is, what aspect of PSC they would like to see researched. PSC is a disease with many unanswered questions.

*9. What "unanswered question" would you like answering about PSC?

*compulsory question

*4. Rank what is most important to you about a PSC treatment: (1= most important; 4=least important)

- How the treatment is administered, such as how long the treatment takes, whether it requires hospitalisation, required doctor visits, etc.
- Whether the treatment is expected to prolong life.
- Whether the treatment is expected to help control symptoms and complications of PSC, including bile duct infections. (not prolong life).
- The side effects associated with treatment.

*5. Right now, if you had to allocate 100 points among each of these treatment areas, how many points would you give each? *(Eg if symptom control is most important to you, followed by cancer prevention, you may wish to allocate: symptoms: 50, cancer 40, death 10. You can allocate the points however you like as long as the total adds up to 100).*

- Control of symptoms and complications of PSC (including bile duct infections)
- Avoidance of death or transplant
- Prevention of cancer

6. Research was published this month concluding that a decrease in ALP levels (a component of regular blood tests for PSC patients) to within the normal range was associated with improved long term survival and decreased risk of needing a liver transplant for PSC patients.
**The normal range refers to expected levels in a healthy person.*

It is possible that some researchers may wish to use ALP levels to determine whether or not a PSC treatment is effective. How confident do you feel that a drug that improves ALP will: (Confident, Not sure, Not confident)

- Reduce the frequency of bile duct infections?
- Prolong your life?
- Improve the quality of your life?
- Control your symptoms?
- Decrease the risk that you'll need a liver transplant?

7. Optional. We welcome any additional comments you may have:

Appendix 2

Table A2.1. Describe the most difficult part of living with PSC: emotional impact responses

Type of emotional impact	Details of emotional impact	Response count	Percentage of emotional impact responses
Uncertainty	Progression, future, needing a transplant, becoming too ill for transplant, rPSC, cancer, repeated infections	201	60.4%
Helplessness	Frustration, low mood, despair, depression, lack of psychological support and burden of having multiple diseases	94	28.2%
Concern about monitoring and care	Concern about inadequate monitoring, invasive monitoring and risks, access to doctors that understand, uncertain diagnosis, tests not reflecting how patient feels, hospitalisation, frequency of interventions and medicines	38	11.4%
Total		333	100%

Table A2.2 Describe the most difficult part of living with PSC: social impact responses

Type of social impact	Details of social impact	Number of concerns reported	Percentage of social impact responses
Witness another suffer	Witness another person suffering, rapidly declining or dying. Effect of PSC on other people	34	37.8%
Invisible illness	Lack of understanding from others/invisible illness	34	37.8%
Social isolation	Social isolation/participation in social activities	17	18.9%
Burden/guilt	Feeling like a burden	5	5.55%
Total		90	100%

Table A2.3. Describe the most difficult part of living with PSC: symptom responses

Type of symptom	Number of concerns reported	Percentage of symptoms responses
Fatigue/feeling unwell	157	43.73%
Itch/jaundice	59	16.43%
Pain	51	14.21%
Symptoms of other diseases and associated medications, symptoms and interventions/monitoring	21	5.85%
Infections	19	5.29%
Sleep problems	15	4.18%
Nausea/loss of appetite/weight loss	12	3.34%
Cognitive effects - memory loss, concentration	8	2.23%
Drug side effects/complications of interventions	7	1.95%
Other liver disease symptoms eg ascites, PH, HE,	7	1.95%
Bloating	3	0.84%
Total	**359**	**100%**

Table A2.4. Breakdown of 'other symptoms' experienced by patients in the previous four weeks.

Other symptoms reported		
Anxiety Ascites Bacterial peritonitis Bleeding gums Bloating Bowel problems* Dark urine Distended upper abdomen	Early menopause Enlarged liver Gallstone Hair loss High blood pressure High cholesterol Joint problems Lightheaded	Nausea* Pain (outside URQ)* Pancreas problems Sleep problems* Shortness of breath Thyroid problems Urinary tract infections Varices

Dry eye Dry mouth	Low platelet count Lyme Disease	Vomiting Weight loss
(included in Figure 2)		

Table A2.5. The most difficult part of living with PSC: day to day activity responses.

Type of impact	Number of concerns reported	Percentage of day to day impact responses
Impact on caring for family/every day activities	38	50%
Impact on employment/ education/ retirement	38	50%
Total	**76**	**100%**

Table A2.6. The most difficult part of living with PSC: economic impact responses.

Type of impact	Number of concerns reported	Percentage of economic impact responses
Financial impact of PSC: reduced hours at work/give up work/time off and knock on impact of childcare/travel/medicines (treatment)	9	75%
Increased cost of financial products across whole range of PSCers	3	25%
Total	**12**	**100%**

Table A2.7a. Summary of 'unanswered questions': Fundamental

Fundamental Questions	Outcome	Number of Asks
What is the cause of PSC or rPSC?	Development of PSC	151
Can an intervention cure PSC? *exercise, novel compound/specific diet/surgery etc	Length of life/ quality of life/ decompensated liver disease/requirement for transplantation	76
How are genetics involved in PSC?	Identification of PSC specific genes/genetic interactions	38
How is PSC linked to other diseases, especially autoimmune diseases, inc IBD?	Identification of and understanding of link between other diseases and PSC	36
Are there different subgroups of PSC and can they be identified?	Identification of clinically distinct phenotypes of PSC/ stratification	34
What is my prognosis	Length of life/ quality of life/ decompensated liver disease/requirement for transplantation	30
Can an intervention* prevent PSC/rPSC? *alcohol, smoking, exercise, coffee, a novel compound, identified risk factors etc	Development (or not) of PSC	24
Can screening* detect PSC?*genetic or other method	Early detection of PSC	19
Can a test or model give an accurate prognosis? (including cancer risk/aggressive PSC)	A prognostic model that accurately reflects the disease progression in individual patients	19
What influences progression of PSC?	Identification of factors that affect PSC development	8
What is the mechanism of action of PSC?	Understanding how PSC develops	7
Can an intervention can repair the damage to the liver caused by PSC? *exercise, novel compound/specific diet/gluten free diet/surgery etc	Length of life/ quality of life/ decompensated liver disease/requirement for transplantation	4
Can you keep me alive?	Length of life/ quality of life/ decompensated liver disease/requirement for transplantation	2
Total		**448**

Table A2.7b. Summary of 'unanswered questions': Self care/help

Care/ Self Help Questions	Outcome	Number of Asks
What can I do to improve my prognosis?	Length of life/ quality of life/ decompensated liver disease/requirement for transplantation	17
What is the best diet for PSC?	Length of life/ quality of life/ decompensated liver disease/requirement for transplantation	7
Best way to educate professionals?	Better PSC knowledge among HCP	4
Care pathways	Consistent access to care and monitoring	3
Non invasive, effective monitoring	Reduced infection risk, reduced pain, quicker monitoring	3
		34

Table A2.7c. Summary of 'unanswered questions': symptoms

Symptoms Questions	Outcome	Number of Asks
What is the cause of my symptoms?	Development of symptoms	9
Can an intervention treat my fatigue?	Reduction in fatigue/increased energy/quality of life	8
What does Urso do?	Understanding of if/how ursodeoxycholic acid affects PSC/colorectal cancer risk	4
What is the most effective intervention to reduce itching?	Reduction in itching/quality of life	3
Does bacterial therapy work in PSC?	Reduction in symptoms/halt progression/reduction in time to transplant/longer life/quality of life	2
Non invasive effective treatment for clearing blockages/stones.	Reduced infection risk, reduced pain, quicker monitoring	2
How to manage symptoms	Reduction in symptoms/halt progression/reduction in time to transplant/longer life/quality of life	2
Can an intervention reduce the number of bile duct infections?	Reduction in duration of infection/increase in time between bile duct infections/quality of life	1
Can an intervention treat HE?	Reduction in number of Bile duct infections	1
Can an intervention treat my sleep disorder?	Improved sleep	1
Do antibiotics work in PSC?	Length of life/ quality of life/ decompensated liver disease/requirement for transplantation/reduction in symptoms.	0
What is the best intervention to reduce upper right quadrant pain?	Reduction in pain/quality of life	0
Total		**33**

Table A2.7d. Summary of 'unanswered questions': Transplant questions

Transplant Questions	Outcome	Number of Asks
Liver availability/liver tissue engineering	Transplant	7
Does liver transplant help PSC and Quality of Life?	Length of life/ quality of life/ decompensated liver disease/requirement for re-transplantation	1
Total		**8**

Table A2.7e. Summary of 'unanswered questions': Miscellaneous questions

Miscellaneous Questions	Number of Asks
Miscellaneous	7
Total	**7**

Table A2.8. Tick the procedures and tests you have ever had:

Answer Options	Response Percent	Response Count
MRI scan	95.1%	331
CT scan	61.8%	215
Bone density scan	48.3%	168
Blood test	98.0%	341
Colonoscopy	87.1%	303
Gastroscopy	46.0%	160
Ultrasound scan	91.7%	319
Liver biopsy	68.4%	238
ERCP	48.3%	168
Fibroscan	16.7%	58
Liver transplant	10.3%	36
Stool sample	45.7%	159
Urine sample	61.8%	215
Saliva sample	15.2%	53
Other (please specify)	5.5%	19
		Total respondents for this question: 348

Table A2.9 Assuming that you were happy with all other aspects of the study, would you participate in a research trial requiring:

Answer Options	NO	YES	N/A
MRI scan	24	284	9
CT scan	34	271	12
Bone density scan	28	277	12
Blood test	14	300	3

Colonoscopy	102	183	32
Gastroscopy	121	164	32
Ultrasound scan	15	297	5
Liver biopsy	135	164	18
ERCP	116	175	26
Fibroscan	54	227	36
Liver transplant	131	98	88
Stool sample	38	265	14
Urine sample	11	299	7
Saliva sample	13	293	11
			Total respondents for this question: 317

Table A2.10 Right now, if you had to allocate 100 points among each of these treatment areas, how many points would you give each? Distribution of allocations

Allocation Frequency	Prevention of cancer	Avoidance of death or transplant	Control of symptoms and complications of PSC (including bile duct infections)
0	10	5	22
1-10	81	44	131
11-20	137	74	145
21-30	206	122	137
31-40	161	164	110
41-50	57	154	78
51-60	9	55	26
61-70	3	25	8
71-80	6	22	8

81-90	4	4	3
91-100	3	8	4
Total	**677**	**677**	**672**