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Signature for Pain Recovery IN Teens (SPRINT): protocol for a multisite prospective signature study in chronic musculoskeletal pain

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ABSTRACT

Introduction Current treatments for chronic musculoskeletal (MSK) pain are suboptimal. Discovery of robust prognostic markers separating patients who recover from patients with persistent pain and disability is critical for developing patient-specific treatment strategies and conceiving novel approaches that benefit all patients. Given that chronic pain is a biopsychosocial process, this study aims to discover and validate a robust prognostic signature that measures across multiple dimensions in the same adolescent patient cohort with a computational analysis pipeline. This will facilitate risk stratification in adolescent patients with chronic MSK pain and more resourceful allocation of patients to costly and potentially burdensome multidisciplinary pain treatment approaches.

Methods and analysis Here we describe a multi-institutional effort to collect, curate and analyse a high dimensional data set including epidemiological, psychometric, quantitative sensory, brain imaging and biological information collected over the course of 12 months. The aim of this effort is to derive a multivariate model with strong prognostic power regarding the clinical course of adolescent MSK pain and function.

Ethics and dissemination The study complies with the National Institutes of Health policy on the use of a single internal review board (sIRB) for multisite research, with Cincinnati Children's Hospital Medical Center Review Board as the reviewing IRB. Stanford's IRB is a relying IRB within the sIRB. As foreign institutions, the University of Toronto and The Hospital for Sick Children (SickKids) are overseen by their respective ethics boards. All participants provide signed informed consent. We are committed to open-access publication, so that patients, clinicians and scientists have access to the study data and the signature(s) derived. After findings are published, we will upload a limited data set for sharing with other investigators on applicable repositories.

Trial registration number NCT04285112.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study simultaneously assesses different critical domains with aid of neuroimaging, immune profiling, somatosensory testing and psychological assessments to characterise the clinical course of pain and function in adolescent patients suffering from chronic musculoskeletal pain.
⇒ A multivariate modelling approach using cross-validation is applied to derive robust and minimally biased prognostic signatures in a high dimensional data set where the number of features (predictors) is larger than the number of observations (sample size).
⇒ The multicentre study design render findings more generalisable.
⇒ Conclusion regarding the effectiveness of the intervention strategies will be limited due to the open-label design and the heterogeneity of interventions.

INTRODUCTION

Up to 5% of adolescents suffer from debilitating, chronic musculoskeletal (MSK) pain[1 2] affecting quality of life, school attendance, mood and family function, and posing a significant economic burden.[3–14] Current treatments for chronic MSK pain are suboptimal.[15] Despite multidisciplinary pain treatment approaches, only 40%–60% of adolescents with chronic MSK pain achieve and sustain improvements in relevant clinical endpoints including pain and functional disability.[16–21] Discovery of robust prognostic markers differentiating patients who recover from patients with persistent pain and disability is essential to develop more resource efficient and patient-specific treatment strategies and to conceive novel treatment approaches that benefit patients whose pain and disability are refractory to current options. Such discovery is particularly pressing for the paediatric population, as the management of paediatric chronic pain is often absent from policy and funding

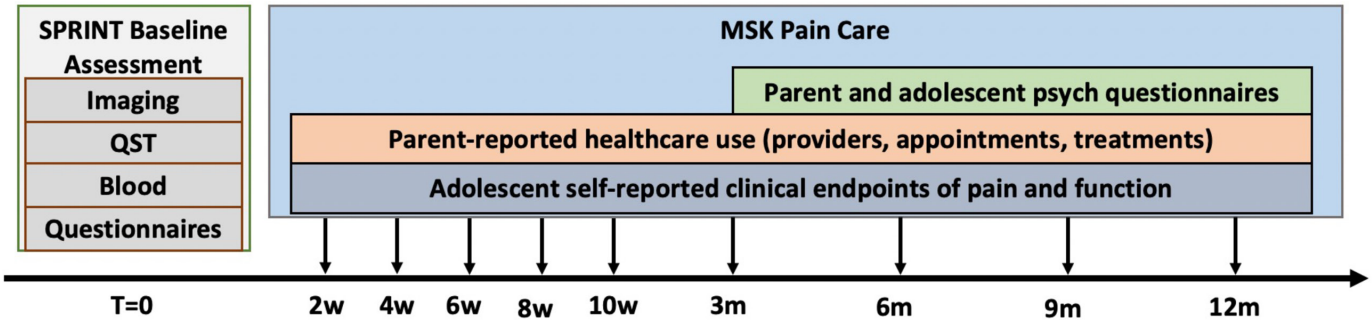

Figure 1 Study sequence. After baseline SPRINT assessment of neuroimaging, quantitative sensory testing, immunological markers in blood and self-report questionnaires, healthcare use and clinical endpoints of pain and function are closely tracked every 2 weeks prior to 3-month follow-up, then at 6 months, 9 months and 12 months. SPRINT, Signature for Pain Recovery IN Teens.

initiatives.[22–24] Moreover, the rate of persistently high levels of pain up to 1 year in adolescents exceeds rates documented in younger peers,[16] and many adolescents with MSK pain continue suffering from pain into adulthood.[3 25] As such, studying MSK pain in adolescence is an urgent priority in pain medicine.[22]

METHODS AND ANALYSIS

Study design

The primary goal of this multisite prospective study, Signature for Pain Recovery IN Teens (SPRINT), is to discover and validate a prognostic signature of recovery versus persistence of pain and functional disability in adolescents with chronic MSK pain undergoing multidisciplinary care, by integrating four major domains: neural, somatosensory, immune and psychological profiles. The approach summarised here entails the study timeline (figure 1) and overview (figure 2). SPRINT was preregistered at ClinicalTrials.gov in February 2020. In the multivariate signature discovery phase, our study teams will enrol adolescent patients (11–18 years) who report to one of three large, multidisciplinary paediatric pain clinics in the USA and Canada. Individuals will be characterised at baseline via neural, somatosensory, immune and psychological metrics. Unbiased machine learning algorithms will derive multivariate models comprising neuroimaging, immune, somatosensory and/or psychological markers that will classify adolescents with MSK pain who will or will not recover after pain treatment intervention as measured by pain and disability levels. Two prognostic signatures will be derived: one for pain and the other for disability. These models will be tested in a second independent prospective cohort of patients in the validation phase. We will estimate the negative prognostic value of the derived signatures for pain and disability non-recovery.

Rationale for study design

Adolescence represents a critical developmental phase for neuronal encoding and plasticity and coincides with the peak onset of chronic pain in childhood. Thus,

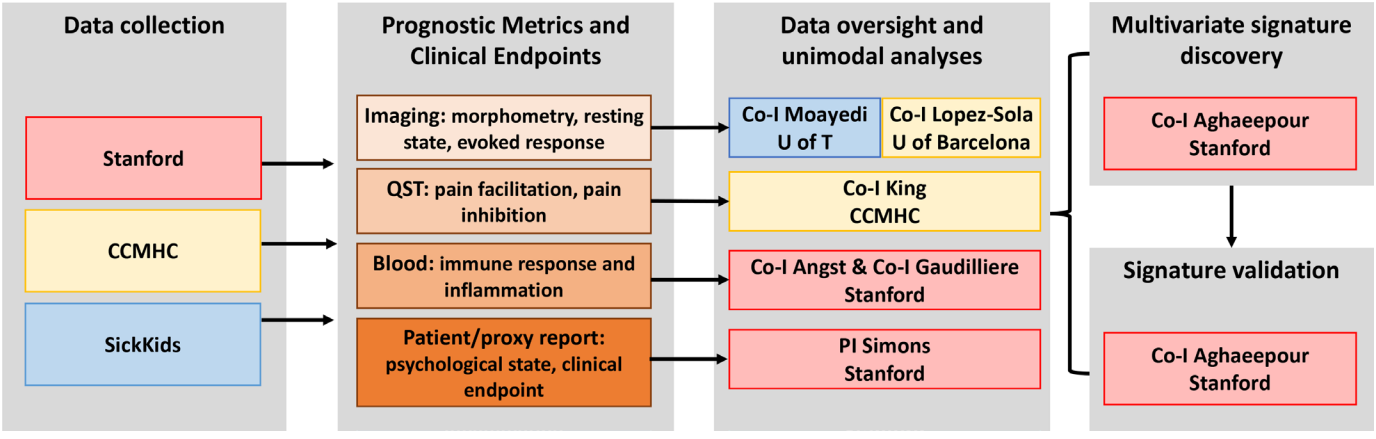

Figure 2 Study overview. A cohort of youth with chronic MSK pain enrol in sprint across three participating sites: Stanford, Cincinnati Children's and Sick Kids in Toronto, Canada. Individuals are thoroughly characterised at baseline. Unbiased machine learning algorithms identify two multivariate models composed of biological and/or psychological markers that predict recovery or persistence of pain and disability in adolescents with MSK pain after multidisciplinary pain treatment. The model will reveal two prognostic signatures to be tested in the R33 validation phase. In an independent cohort of patients, we will capture our metrics at clinic presentation to test the positive and negative prognostic value of the signatures predicting persistence of MSK pain and disability after multidisciplinary pain treatment. MSK, musculoskeletal.

elucidating multiple markers or a 'signature' of recovery versus persistence in chronic MSK pain during this sensitive period is critical for risk stratification and targeted treatment for the more effective prevention of lifelong MSK pain.[26–29] Emerging evidence indicates that brain structure and function, sensory profiles (pain facilitation/inhibition)[21 30] and psychological factors[16 31 32] distinguish recovery versus persistence of pain in adolescents. Additional findings in adult chronic MSK pain patients demonstrate pre-existing abnormalities and pain-related changes in the central nervous system as evidenced by immune,[33–35] brain structure and function,[36–38] somatosensory[39–45] and psychological markers (eg, pain catastrophising).[46–48] While cogent, these studies are limited by small sample sizes, focus on a single metric (eg, imaging) and report associations rather than predictive values. Given that chronic pain is a biopsychosocial process,[49] the discovery and validation of a robust prognostic signature for recovery versus persistence requires measurements across multiple dimensions in the same patient cohort, in combination with a suitable multivariate computational analysis pipeline including cross-validation, for the extraction of reliable results from a multilayered and complex dataset.

Participants and setting

Two cohorts of patients, one for the multivariate model discovery and the second for independent model validation, are recruited from three academic medical centres specialising in paediatric pain management. The three centres are comprehensive multidisciplinary programmes that collectively evaluate over 800 new patients with chronic pain each year. Stanford Children's Health Pediatric Pain Management Center (PPMC) houses multiple ambulatory paediatric pain clinics across the San Francisco Bay Area. The Toronto Hospital for Sick Children (SickKids) Chronic Pain Clinic is the largest paediatric pain clinic in Canada. Cincinnati Children's Hospital Medical Center (CCHMC) is one of the larger specialised multidisciplinary centres for paediatric chronic pain management in the USA. PPMC and SickKids patients are recruited in ambulatory clinics. CCHMC patients are recruited in ambulatory clinics and when hospitalised in the Functional Independence Restoration Program.

Research staff review patient charts for eligibility via electronic medical record (EMR) before their clinic appointments and notify clinicians (physicians and psychologists) of potentially eligible patients. The clinician extends an offer to the patient and caregiver(s) to meet with a research coordinator to learn about ongoing clinical research studies, including SPRINT. If the patient and caregiver(s) agree, a research coordinator meets with the family to describe SPRINT. If interested, the patient undergoes a second, more thorough screening to ensure eligibility. Text Box 1 details the inclusion and exclusion criteria.

Measures

Questionnaire, self report and somatosensory (quantitative sensory testing (QST)) data are collected and managed using Research Electronic Data Capture (REDCap) hosted at each respective site (Stanford, Cincinnati Children's and SickKids).[50 51] REDCap is a secure (encrypted, HIPPA-compliant), web-based software platform designed to support data capture for research studies, providing: (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical software packages; and (4) procedures for data integration and interoperability with external sources. MRI data are collected and managed via Flywheel, hosted at the Lucas Centre, Stanford University. Flywheel is a virtual platform designed specifically for the curation, archiving, preprocessing, and analysis of both structural and functonal MRI data. Blood-derived biological data are archived at Stanford Biobank.

Clinical endpoint and signature candidate measures are detailed in table 1 by domain, measure name, reporter/test type and time point.

Clinical endpoints

Pain

Pain intensity is measured using a visual analogue scale (VAS) and numerical rating scale (NRS). VAS ratings of pain intensity and unpleasantness involve moving a slider from no pain intensity/not at all unpleasant to most intense pain imaginable/most unpleasant imaginable without visible numerical values. The distance on the marker signifies a numerical value (range 0–10, increments 0.1) are only visible to the experimentor. The VAS has been demonstrated to exhibit ratio scale properties.[52 53] VAS is the primary pain metric.

Given the wide use of NRS in clinical practice, pain is also assessed using the NRS from the Brief Pain Inventory.[54] Pain is rated on an 11-point integer scale ranging from 0='no pain' to 10='pain as bad as you can imagine' for *current* pain, for *worst*, *least* and *average* pain during the last 7 days. NRS is the secondary pain metric.

Functional disability

Functional impairment is measured using the Functional Disability Inventory (FDI).[28] The FDI consists of 15 items that are rated on a 5-point Likert scale ranging from 0 (no trouble) to 4 (impossible to do). The FDI is widely used in paediatric pain research and is recommended as the gold standard to assess physical functioning for school age children and adolescents in clinical trials of chronic pain.[5556]

VAS pain intensity, VAS pain unpleasantness and functional disability are completed online through REDCap at *baseline* and at *2-week intervals* through *3-month follow-up* (primary). Assessment of clinical endpoints resume at *6-month, 9-month and 12-month follow-up* (secondary/exploratory). All data collection intervals are detailed in figure 1.

Table 1 Tests, measures and timeline of events for the SPRINT study

Domain	Questionnaires or assessment	Type	Timeline of events			
			Screen	Baseline	Bimonthly	3-month follow-up
Clinical endpoints						
Functional disability	Functional Disability Inventory (FDI)[104]	Q	×	×	×	×
Pain intensity	Average pain over the past week (0–100 visual analogue scale (VAS))[105]	Q	×	×	×	×
Prognostic metrics – demographic, physical and psychological factors						
Demographic	Age (years), sex (M/F), socioeconomic status	Q		×		
Pain parameters – child	ICD-11 diagnosis	M		×		
	Body Map	Q		×		×
	McGill Pain Questionnaire-Short Form[106]	Q		×		
	Revised Pain Symptom Assessment Tool (R-PSAM)	Q		×		
	Child Pain Questionnaire (CPQ)	Q		×		
	Pediatric Pain Screening Tool (PPST)	Q		×		
	Brief Pain Inventory – Pain Severity & Interference[NIH]	Q		×		×
Physical functioning and QoL	Pediatric Quality of Life (PedsQL) Inventory[NIH]	Q		×		×
	Adverse Childhood Experiences Questionnaire	Q		×		
	PROMIS-Fatigue	Q		×		
	Pubertal Development Scale[107]	Q		×		
	Height/weight (T)	A		×		
Sleep	Adolescent Sleep Wake Scale[NIH]	Q		×		×
Psychological						
Catastrophising	Pain Catastrophizing Scale[108] for child[NIH]	Q		×		×
Anxiety/depression	Generalized Anxiety Disorder 2-item (GAD-2)[NIH]	Q		×		×
	Patient Health Questionnaire-2 (PHQ-2)[NIH]	Q		×		×
	PROMIS Anxiety, Depression[109 110]	Q		×		
Fear of pain	Fear of Pain Questionnaire[111] for child	Q		×		
Other	Pain Stages of Change Questionnaire-Adolescent[112]	Q		×		
	8-item Chronic Pain Acceptance Questionnaire	Q		×		
	Bodily Threat Index	Q		×		
Global satisfaction with treatment	Patient Global Impression of Change[NIH]	Q		×		×
Substance use screener	NIDA Modified Assist Tool-2[NIH]	Q		×		×
Parent measures	Parent Health	Q		×		
	GAD-2[NIH]			×		×
	PHQ-2[NIH]			×		×
	Parent Risk and Impact Screening Measure	Q		×		
	Adult Responses to Children's Symptoms (ARCS) – Protect Subscale (ARCS-Protect*)	Q		×		
	Diagnostic Uncertainty	Q		×		
	10-item Parent Psychological Flexibility Questionnaire	Q		×		
	Pain Catastrophizing Scale for parents[NIH]	Q		×		×
Prognostic metrics – immune						
Cell abundance	Mass cytometry (MC): abundance of 24 different immune cell types	T		×		
Basal cell function	MC: cell-type specific activity of signalling molecules/ cascades (phosphorylation) at basal state	T		×		
Evoked cell function	MC: cell-type specific activity of signalling cascades in response to LPS, IL2, IL4 and IL6	T		×		

Continued

Table 1 Continued

Domain	Questionnaires or assessment	Type	Timeline of events			
			Screen	Baseline	Bimonthly	3-month follow-up
Prognostic metrics - imaging						
Morphometry	T1-weighted 3D magnetisation-prepared rapid gradient echo scan[113]	T		×		
Resting state	Simultaneous multislice echo planar imaging (SMS-EPI) resting state sequence	T		×		
Evoked brain activation	4 min multisensory task SMS-EPI sequence (same parameters as resting state)[114]	T		×		
Prognostic metrics - quantitative sensory testing						
Pain facilitation	TP: gradual increase in pain intensity of a repeated (at a constant rate) painful stimulation.	T		×		
Pain inhibition	CPM: reduction of pain sensitivity (test stimulus) following a cold-water immersion (conditioning stimulus at a remote contralateral site).	T		×		
Multidisciplinary pain care						
Pain treatment history	Healthcare Use History	Q		×		
Current pain treatment	Healthcare Use Diary	Q		×	×	×

FDI and VAS: as part of the inclusion criteria, FDI patients are moderate to severe (FDI=13–60)[72] at baseline. FDI will be reassessed at the 3-month follow-up to determine if disability has: (A) improved (eg, indicating recovery based on a reduction to mild disability (0–12)) or (B) persisted (eg, indicating no recovery based on moderate to severe disability (13–60).[72] Similar strategy will be used for VAS in which patients will need to have moderate to severe pain at baseline (VAS=30–100).[115] Additionally, pain intensity (VAS) will be reassessed at the 3-month follow-up to determine if disability has: (A) improved (eg, indicating recovery based on reduction to mild pain (0–29)) or (B) persisted (eg, indicating no recovery based on moderate to severe (30–100).[115]
Prior and current treatments: information about prior and current treatments (and other heathcare usage)[116] will be collected to track different types of pain treatment (pharmacological, physical and psychological therapies). Parents will complete these surveys.
Other abbreviations: part of the NIH Common Data Elements.
CPM, conditioned pain modulation; ICD-11, Eleventh revision of the International Classification of Diseases; M, medical record; Q, self-report questionnaire; SPRINT, Signature for Pain Recovery IN Teens; T, test.

Signature candidates

Demographic, physical and psychological indicators

Demographic, physical and psychological measures are completed through REDCap or derived from the EMR. Measures include NIH Common Data Elements (CDEs; https://cde.nlm.nih.gov/home) deployed in all studies funded via the National Institutes of Health (NIH) Helping End Addiction Long-Term (HEAL) initiative, along with study-specific questionnaires (see table 1 for detailed measures list). NIH HEAL CDE domains include pain intensity, pain interference, physical functioning/quality of life, sleep, pain catastrophising, depression, anxiety, global satisfaction with treatment and substance use. SPRINT study-specific candidate markers that span demographic, physical functioning/quality of life and psychological domains were derived from established or emerging evidence in the realm of pain risks and include adverse childhood experiences,[57 58] readiness to take a self-management approach to pain[16] and parent behaviour in the context of child chronic pain.[59 60]

Collection of blood for biobanking and immune profiling by mass cytometry

A phlebotomist collected 32.5 mL of venous blood from each participant using a standard venipuncture technique into one 10 cc tube containing sodium heparin (BD 366480), two 10 cc tubes containing dipotassium EDTA (BD 366643) and one 2.5 cc PAXgene RNA isolation tube (BD 762165). The 10 cc sodium heparin tube is maintained at ambient temperature until further processing with mass cytometry. Within 2 hours of collection, heparinised whole blood samples (1 mL) are aliquoted into Smart Tubes (Smart Tube Inc, Las Vegas, Nevada, USA) for stimulation and fixation of cells according to well-established protocols.[61] Each custom-manufactured Smart Tube is preloaded with a lyosphere either containing 1 µg lipopolysaccharide (Invivogen TLRLPEKLPS), 1 µg recombinant human interleukin-1β (Invitrogen RIL1BI), a cocktail of 100 ng each recombinant human interleukin-2 (Peprotech 200–02), interleukin-4 (Peprotech 200–04), interleukin-6 (Peprotech 200–06) or excipient only (unstimulated). After processing, Smart Tubes are immediately stored at −80°C. Plasma and buffy coat are obtained from the EDTA tubes, and mRNA is collected using PAXGene RNA tubes, which are banked for future genetic analysis. External sites ship overnight in temperature tracked boxes with dry ice to Stanford Biobank in batches of 14 participants for storage.

Structural MRI (sMRI) and functional MRI (fMRI)

Participants undergo an MRI session lasting approximately 90 min. On arrival, participants and a caregiver

complete the participant screening form to ensure participant safety prior to entering the 3T MRI scanner. Coordinators train participants on the multisensory task[62] with an instructional presentation and practice. Due to using different MRI magnets at each site (Siemens Prisma at University of Toronto, GE Premier (Software RX27.0) at Stanford, Philips Ingenia Elition at Cincinnati), the imaging protocol was piloted and acquisition sequence parameters were aligned across sites for maximum consistency given the hardware differences at sites. Acquisition sequences, scanner-specific field maps and shimming is detailed in table 2. During the resting state fMRI scan participants are instructed to keep their eyes open, not think of anything in particular and are presented with a black screen with white crosshair, across all three sites. The multisensory evoked task consists of four trials of alternating 30 s simultaneous multisensory motor stimulation (visual, auditory and tactile–motor during finger opposition task) and rest periods of 22.5 s on average (20–30 s). Following each multisensory stimulation period and after a short interstimulus interval of 3 s on average (2–4 s), a 10 s rating period is shown where patients answer the question 'How unpleasant was the sensory experience you just experienced?' using computerised VAS ranging from 'not at all unpleasant' (0) to 'the most unpleasant you can imagine' (100).[62]

Quantitative sensory testing (QST)

All tests are conducted by researchers at each centre who have received equivalent training, and the researchers undergo regular calibration across sites. The patient sits in a comfortable position. A standardised set of instructions are read, and a practice trial of each test is performed on the experimenter for demonstration purposes to ensure a participant understands the procedure. The test protocol is based on standardised sequences from other groups and our own[63–67] and includes two primary QST measures and several secondary QST measures (table 3).

Primary measures

Dynamic QST modalities that have predicted persistent MSK pain outcomes include enhanced temporal summation (TS) in adults[45] in addition to impaired conditioned pain modulation in adults[45] and children.[21] These measures reflect central modulation and will be used as our primary predictors of recovery versus persistence in adolescents with chronic MSK pain. TS, reflects an increase in reported pain intensity to a repeated train (at a constant rate) of stimuli using a standardised pinprick stimulator (PinPrick stimulator, MRC Systems) either at 256 mN or 128 mN (if the 256 mN could not be tolerated). TS is quantified by comparing VAS ratings of single pinprick stimulation (VAS_1) to the VAS rating following a 1/sec train of 10 repeated pinprick stimuli (VAS_{10}) applied within a small area. Conditioned pain modulation (CPM) reflects an alteration in pain sensitivity to a test stimulus by the simultaneous application of a painful conditioning stimulus at a contralateral body site. For the SPRINT protocol, CPM is evaluated using pressure pain threshold (PPT) as the test stimulus and a cold conditioning stimulus. Specifically, PPT is assessed at the non-dominant trapezius with a hand-held algometer (AlgoMed, Medoc) at three periods. First, baseline PPT is collected (three trials) in the absence of the conditioning stimulus. Then, PPT (two trials) is collected during the conditioning stimulus, immersion of the dominant hand into a circulating 10.0°C water bath (Techne TE-10D Thermoregulator, B-18 Bath and RU-200 Dip Cooler). Finally, postimmersion PPT (two trials) is assessed 10 s after removal of the participant's hand from the water bath. CPM is quantified by comparing the change in PPT (from baseline) during and following cold immersion.

Secondary measures

Several secondary measures are used to characterise somatosensory function. First, mechanical detection threshold (MDT) is used to assess the ability to detect tactile sensations. Using a series of von Frey filaments (Aesthesiometer II Filaments, Somedic), MDT provides quantitative evidence of altered activity in low threshold mechanoreceptive fields, which could indicate the presence of neuropathy. Second, a series of weighted pinprick stimulators (PinPrick stimulator, MRC Systems) is used to assess mechanical pain threshold, which could provide evidence of neuropathy or mechanical allodynia. Third, the same weighted pinprick stimulators are used for suprathreshold ratings of pain intensity (mechanical pain sensitivity (MPS)). Fourth, PPT is assessed with a hand-held algometer to test the first sensation of blunt pressure at three separate, bilateral sites (trapizious, thenar and knee). Lastly, participants undergo a cold pressor test at the end of the QST assessment, which involves placing their hand into cold water (8.0°C) and reporting the first sensation of cold pain (cold pain threshold) and as long as they can tolerate (cold pain tolerance; up to 180 s). Cold pain intensity is collected following removal of their hand.

Multidisciplinary chronic pain care

Pain care utilisation including appointments with general and specialist medical, physical therapy, psychology/mental health providers, alternative healthcare practitioners, medications and hospital admissions is tracked through REDCap assessments deployed to the caregiver to complete at baseline, biweekly until 3-month follow-up and then subsequently at 6-month, 9-month and 12-month postbaseline.

Procedures

Study visit

Total study visit time is approximately 4 hours, including breaks between data collection activities. In order to maximise retention of our paediatric chronic pain patients, participants are allowed to skip any assessments that they are unable to tolerate or testing may be divided into two sessions.

Table 2 MRI parameters

	Stanford	Cincinnati	Toronto
Scanner manufacturer	**GE premier**	**Philips Ingenia Elition**	**Siemens Prisma**
Structural MRI			
T1 weighted			
Sequence	FSPGR	ME-MPRAGE	ME-MPRAGE
TR	6.8 ms	10 ms	2530
TI	0.6 ms	1100	1100
TE	3 ms	Multiecho	Multiecho
FOV	256×256 mm	256×256 mm	256×256 mm
Matrix	256×256	256×256	256×256
Voxel dimensions	1 mm^3	1 mm^3	1 mm^3
Number of Slices	160	200	176
Diffusion weighted			
TR	3600 ms	4154 ms	3600 ms
TE	80 ms	71 ms	80 ms
FOV	220×220 mm	220×220 mm	220×220 mm
Matrix	110×110	112×110	110×110
Voxel dimensions	2 mm^3	2 mm^3	2 mm^3
Number of slices	62	56	64
In-plane acceleration	Acceleration phase=2	SENSE=2	GRAPPA=2
Multiband factor	2	2	2
Number of diffusion encoding directions	60	64	60
Number of B0s	10	7	10
T2 weighted			
TR	3390 ms	3390 ms	3390 ms
TI	1100	1100	1100
TE	155 ms	388 ms	244
FOV	256×256 mm	256×204 mm	256×256 mm
FOV phase	90%	79.7%	79.7%
Matrix	512×512	256×204	256×256
Voxel dimensions	0.5 mm^3	1 mm^3	1 mm^3
Number of slices	344	176	176
In-plane acceleration	Acceleration phase=2	SENSE=2	GRAPPA=2
Functional MRI			
Simultaneous multislice (SMS) echo planar imaging (EPI)			
Task and resting state			
Orientation	Oblique, aligned to OFC	Oblique, aligned to OFC	Oblique, aligned to OFC
TR	1500 ms	1500 ms	1500 ms
TE	30 ms	35 ms	30 ms
Flip Angle	70°	70°	70°
FOV	220	220	220
Matrix	88×88	88×87	88×88
Number of slices	57	57	57
Voxel dimensions	2.5 mm^3	2.5 mm^3	2.5 mm^3
In-plane acceleration	Acceleration phase=2	SENSE=1	GRAPPA=1
Multiband factor	3	3	3

Continued

Table 2 Continued

Scanner manufacturer	Stanford GE premier	Cincinnati Philips Ingenia Elition	Toronto Siemens Prisma
Volumes (rs-fMRI)	257	257	257
Volumes (task)	180	180	180

FOV, Field of View; TE, Time to Echo; TI, Inversion Time; TR, Repetition Time .

Consent

A member of the research staff obtains informed parent consent and youth assent/consent and confirms the patient has refrained from short-acting analgesic medications for at least 4 hours prior to the visit due to its potential impact on brain activation during MRI and sensory response during QST. The consent process takes approximately 30 min.

Baseline assessment

Adolescents and a caregiver attend an in-person study visit across 1 or 2 days, depending on site logistics and participant availability. After informed consent/assent procedures, the adolescent and caregiver complete questionnaires (table 1), and a blood draw from the adolescent is obtained. Then, adolescents undergo a single MRI session followed by QST assessment.

Chronic pain treatment

After initial evaluations, patients undergo multidisciplinary pain management treatment through their clinical recruitment site or locally. Multidisciplinary treatment for primary MSK pain involves medical, physical therapy, pain psychology and complementary treatments.[68] As indicated and per standard practice, medical management includes: diagnostic studies, medications and injections as indicated and education about pain and is treatment is provided as per standard practice. Moreover, patients receive some level of pain science education.[69] Physical therapy treatment is individually tailored and based on the Guide to Physical Therapy Practice 3.0 (guide.apta.org), consisting of: (1) therapeutic exercise, (2) balance and proprioception, (3) strength training/endurance and (4) use of modalities (eg, heat/cold pack, Transcutaneous Electrical Nerve Stimulation (TENS)). Pain psychology is grounded in cognitive–behavioural therapy and includes sessions focused on education about the biopsychosocial model and pain processing, goal setting, pain coping skills training (eg, relaxation) and cognitive restructuring.[70] Complementary treatments span massage, herbal remedies, acupuncture, etc. As complete uniformity even within clinic is not possible, the treatments rendered are carefully tracked. Biweekly assessments completed by the caregiver track pain care utilitisation through 3-month follow-up and then every 3 months for 6-month, 9-month and 12-month follow-up. We anticipate *treatment variability*. Although each site provides standardised treatments to adolescents with chronic MSK in their pain clinics, we have a rigorous biweekly electronic tracking of patient service use (Healthcare Use Diary; see online supplemental appendix).

Clinical endpoint tracking

Biweekly assessments track clinical endpoints of pain and functional disability through 3-month follow-up to categorise adolescents recovered versus persistent (primary). Additional assessments of clinical endpoints are collected

Table 3 Expanded quantitative sensory testing methods

Procedure	Equipment and device(s)	Primary site	Secondary site
Mechanical detection threshold	Aesthesiometer II Filaments*	Control hand (dorsum – thumb web)	Most affected site
Mechanical pain threshold	PinPrick stimulator†	Control hand (dorsum – thumb web)	Most affected site
Mechanical pain sensitivity	PinPrick stimulator†	Control forearm (ventral)	
Pressure pain threshold	AlgoMed‡	Bilateral thenar Bilateral trapezius Bilateral knee	–
Temporal summation	PinPrick stimulator†	Control forearm (ventral)	Most affected site
Conditioned pain modulation	AlgoMed‡	Non-dominant trapezius	–
	Techne Water Bath*	Immersion of dominant hand	–
Cold pain tolerance	Techne Water Bath§	Immersion of dominant hand	–

*[a]Somedic (http://somedic.com/en/).
†MRC Systems GmbH (https://www.mrc-systems.de).
‡Medoc (https://medoc-web.com).
§Techne (Techne TE-10D Thermoregulator (SK-01 262–05); B-18 Litre, Unheated (SK-16 112–01); RU-200 Dip Cooler (SK-14 576–05); Finger Guard for Pain Batch (SK-00383YU)).

at 6-month, 9-month and 12-month follow-up (secondary/exploratory).

Analysis plan

Deriving recovery versus persistence for clinical endpoints

Pain and function

Defining recovery versus persistence of pain and function can be approached from a categorical (cut-off score or metric of clinical improvement (eg, 30%)) or continuous (trajectory) standpoint.

Categorical

Category driven classification uses a clear cut-off scores for what is considered recovery for pain (VAS rating <30)[71] and function (FDI score <13)[72] or sets a threshold using a widely accepted metric of clinical improvement of, for example, 30%.[73] The cut-off score is a single value not tied to baseline status, and thus, critical information is lost regarding degree of improvement. The metric of clinical improvement addresses this issue but an individual could remain within the same clinical range (eg, moderate, severe), yet still evidence a 30% improvement. Current recommendations suggest a combined categorical approach that merges distribution-based methods (cut-off scores) and responder analysis (metrics of clinical improvement).[73–75] This combined categorical approach has also been used within paediatric chronic pain to examine clinically meaningful change in functional disability among youth with juvenile fibromyalgia after pain psychology.[76] The advantage of this approach is the well-established nature of these values, but they are static outcomes that likely do not reflect the complexity of recovery or persistence over time.

Continuous

Continuously driven classification can be derived using multiple time points to create a trajectory of recovery/persistence for pain and function. Trajectories provide the opportunity to model the complexity of response over time that may or may not neatly fit into a predefined category. Our prior work examining response to intensive interdisciplinary treatment in adolescents with chronic pain derived two response groups for disability (responder/nonresponder) and three groups for pain (early responder, late responder and non-responder).[16]

The data collected in this study will enable the possibility of both categorical and continuously driven classification.

Deriving signature candidates

Demographic, physical and psychological

All values are verified for validity (eg, fall within the expected value ranges), scores standardised as necessary (eg, PROMIS tools) and totals for measures are calculated (eg, Pain Catastrophizing Scale for Children).

Mass cytometry (MC) and derivation of immune features

Mass cytometry analysis

On the day of analysis, fixed whole blood samples are thawed, processed and stained for mass cytometry analysis using a protocol developed in house.[77 78] Briefly, after red blood cell lysis (Smarttube thaw-lyse buffer), peripheral leukocytes are barcoded using a combination of six palladium metal isotopes, allowing for simultaneous analysis of up to 20 samples. This step substantially reduces sample-to-sample experimental variability due to antibody staining and instrument sensitivity.[79 80] Barcoded samples are pooled and stained with metal-conjugated antibodies using a 40–50 plex antibody panel. Antibodies are either obtained preconjugated from the manufacturer (Fluidigm) or conjugated in-house with the appropriate metal isotopes. Purified unconjugated antibodies in protein-free PBS carrier are labelled using the MaxPAR antibody conjugation kit (Fluidigm) according to the manufacturer's instructions. All antibodies used in the analysis (conjugated in-house as well as those obtained preconjugated) are titrated and validated on samples that are processed identically to the samples used in the study. Stained samples are analysed on a Helios mass cytometer instrument (Fluidigm) at a flow rate of 600–800 cells/s. The output FCS files are normalised and debarcoded using MatLab-based software, as previously described and uploaded to the Cell Engine (https://cellengine.com, Primity Bio, Fremont, California, USA) flow cytometry analysis platform.

Derivation of immune features

After normalisation of the single-cell mass cytometry data, major innate and adaptive immune cell subsets are identified using an agnostic clustering algorithm or a manual gating strategy. Three categories of immune features are derived:

Cell frequency immune features

Immune cell frequencies are expressed as a percentage of gated singlets in the case of neutrophils and as a percentage of mononuclear cells in the case of all other cell types.

Endogenous signalling immune features

Cell type specific endogenous signalling immune features are derived from the mass cytometry analysis of unstimulated blood samples. The basal (endogenous) signalling activity of multiple intracellular proteins (eg, the site-specific phosphorylation (p) signal pSTAT1, pSTAT3, pSTAT5, pSTAT6, pNFkB, pMAPKAPK2, pP38, prpS6, pERK1/2 and pCREB and the total IkB signal) is simultaneously quantified for individual immune cell. For each cell type, endogenous signalling immune features is calculated as the median signal intensity (arcsinh transformed value) of each signalling protein activity. Selected intracellular proteins are sentinel components of the signalling cascades downstream of Toll-like (NFkB, IkB, MAPKAPK2, P38, rpS6, ERK1/2 and CREB) and cytokine receptors (STAT 1, 3, 5 and 6).

Evoked signalling immune features

Cell type specific evoked signalling immune features are derived from samples stimulated with extracellular ligands (LPS, IL-1β, IL-2/IL-4/IL-6). The activities of the same signalign proteins in response to each stimulation

condition is quantified on a per cell basis. For each cell type, evoked signalling responses are calculated as the difference in median signal intensity (arcsinh transformed value) of each signalling protein between the stimulated and unstimulated conditions.

Magnetic resonance imaging

Data are uploaded to a FlyWheel repository, where they undergo standard quality assurance/quality checks with MRIQC. Structural (T1 and T2 weighted) and functional MRI (task and resting state) data are then processed with fMRIprep.[81] Structural data are skull stripped, normalised to a standard space template and segmented into tissue classes (CSF, WM and GM), and then undergoes surface reconstruction (with FreeSurfer – see Morphometry, further). fMRI data undergo motion correction, susceptibility distortion correction and coregisteration to the normalised T1-weighted image. Confound regressors (based on motion and non-neuronal signal) are created. Data are then smoothed with a 3D Gaussian kernel. Data then undergo independent component analysis decomposition for denoising purposes using a Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) in FSL.[82] The resultant components are then be fed to a classifier (ICA-FIX)[83 84] trained on a subset of data from each site to identify components that comprise of noise and those that comprise of signal. The classifier identifies and removes signal from components that are classified as noise. The data are then reconstructed and ready for statistical analysis.

First-level single-subject analysis for the multisensory activation task

We use a massive univariate general linear model (GLM) analysis approach as implemented in freely available neuroimaging software (eg, SPM12 and FSL) to estimate, for each patient, brain responses to the multisensory task. Regressors modelling the multisensory activation condition are created by convolving each period of interest (multisensory activation) in the time series fMRI data with a canonical haemodynamic response function. The model includes motion regressors and appropriate regressors for outlier data points (to control for artefacts in time series data). Parameter estimates are calculated at each voxel using the GLM. A high-pass filter is applied to remove low-frequency signal fluctuations (1/180 Hz), and global intensity normalisation is applied by dividing each voxel in a volume by the mean of all brain voxels in that volume. We calculate contrast images for the multisensory condition of interest (beta values for the multisensory regressor) for each patient. The resulting activation contrast image patterns are extracted as matrices, which are used in the prediction model.

Resting state networks

Data are parcellated into 180 subregions based on a an atlas derived by identifying brain regions based on convergent multimodal evidence—the Glasser 2016 Atlas.[85] A whole brain ROI-to-ROI correlation analysis is performed, and the resultant matrix for each participant is submitted to the prediction algorithm. Different parcellation atlases may be adopted, as these are developed.

Morphometry

Grey matter structure is assessed using cortical thickness analysis in FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). Cortical thickness values are computed for every subregion in the brain based on the Destrieux 2009 atlas.[86] Subcortical volumetric segmentation values are derived from the FreeSurfer subcortical processing stream, which is based on the Harvard-Oxford Subcortical Atlas.[87] Cortical thickness values and subcortical volumes are submitted to the prediction algorithm. As analytic tools evolve, we may use other validated software to ensure that analyses are considered state of the art at the time that they are executed.

Diffusion-weighted imaging

Diffusion data will undergo standard preprocessing in FSL's Diffusion Toolbox. Data will first undergo distortion and motion correction with Topup. Next, we derive a whole brain structural connectivity matrix on data that have been processed for tractography using BEDPOSTx. The brain is parcellated into 180 subregions using the Glasser 2016 Atlas. An ROI-to-ROI connectivity matrix is produced for each participant, and submitted to the prediction model.

Quantitative sensory testing

In order to operationalise pain facilitation (TS), the intensity from this single pinprick stimulus (VRS1) is compared with the perceived intensity following a 1/sec train of 10 repeated stimuli of the same intensity (VRS10), applied within a small area of 1 cm^2. Patients are also asked if the stimulus feels the same, more intense (ie, sensitisation) or less intense (ie, habituation). TS is calculated as a change score (VRS10-VRS1) in which higher change score reflects greater facilitation. In order to operationalise endogenous pain modulation (Conditioned Pain Modulation), changes in mean PPT and per cent change in PPTh from baseline [(PPTh × seconds – PPThbaseline) / PPThbaseline) × 100] are calculated. We examine changes in PPTh during conditioning to identify increases in PPT that reflect the degree of inhibition and reductions in PPT that reflect facilitation.

Signature detection

The prognostic multivariate signature potentially includes blood (immune markers), psychophysiological (QST), imaging (brain structure and function) and patient report (demographic, physical and psychological) measures. This high dimensional dataset composed of a large number of data points (eg, millions of cells per patient in case of mass cytometry data, hundreds of thousands of voxels in MRI) pose unique computational challenges that cannot be addressed by traditional bioinformatics tools.[88] The detection of the signature occurs via derivation of a multivariate model with aid of the Elastic

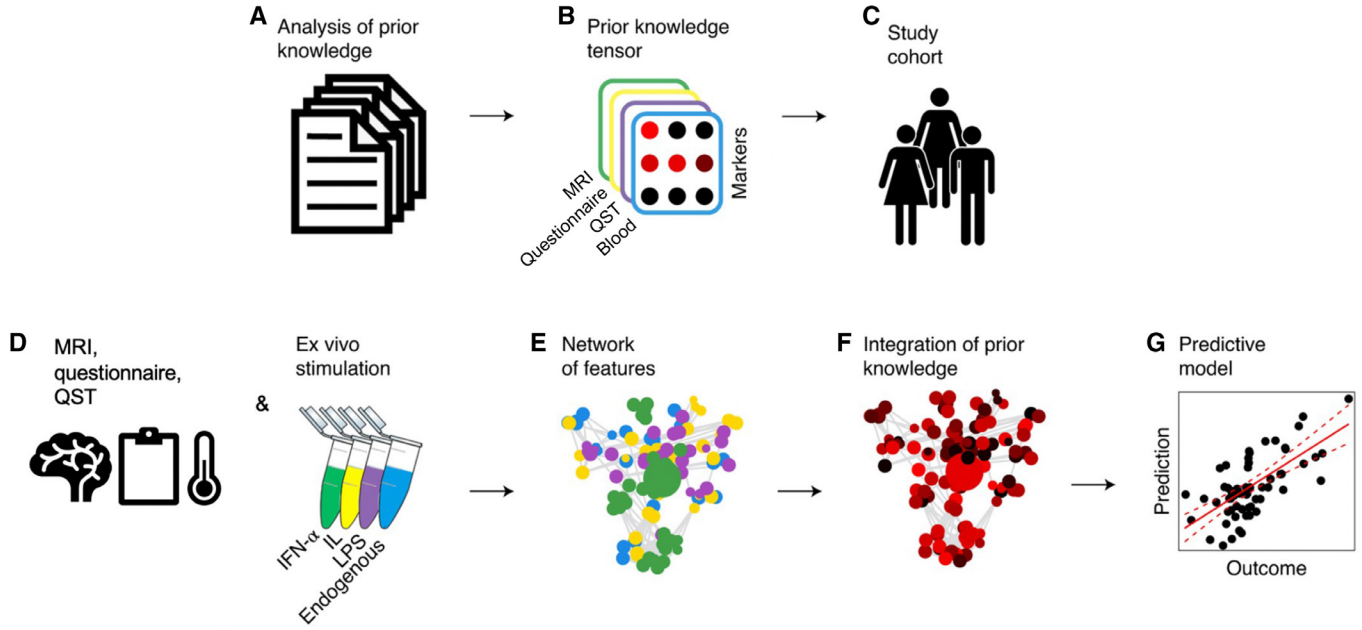

Figure 3 The Elastic Net (EN) analysis pipeline. Neuroimaging (MRI), quantitative sensory testing (QST), immunological (blood) and self-report questionnaire prior knowledge for each feature is extracted by a panel of experts (A) and encoded into a prior knowledge tensor to guide the model optimisation process (B). Individuals within the study cohort (C) provide MRI, questionnaire and QST data, and blood samples, which are subsequently preprocessed (MRI), scores calculated (questionnaire, QST) or stimulated with ligands ex vivo to activate various signalling pathways of the immune system (blood) (D). This produces a a complex set of biopsychosocial features for the prognostic signature (E). This dataset is then fed into the EN algorithm (F) for prognostic modelling of the outcome of interest (G).

Net (EN) algorithm.[89] We anticipate that our study will generate a large and highly correlated dataset. For analysis of the immune system, traditional univariate (eg, significance analysis of microarray[90] or multivariate (eg, least absolute shrinkage and selection operator (LASSO)[91] approaches are often limited, as they do not account for the intercorrelated nature of the data.[89 92 93] Members of our group recently developed an adapted EN algorithm for immunological data (iEN analysis pipeline.[94] Figure 3 depicts our analysis pipeline and is adapted from iEN.[94] This novel penalised regression method is derived from the EN algorithm.[90 95 96] The iEN algorithm is particularly adapted to the analysis of highly correlated datasets, as it eliminates redundant parameters but retains interrelated parameters. In a side-by-side comparison, the iEN algorithm outperformed the most common alternative predictive methods including the EN,[90] Support Vector Machine,[97] LASSO, random forest[98] and KNN.[99] Other psychophysiological, imaging and patient reported modalities are directly integrated into these models using stack generalisation, as previously described.[100 101]

Dependence on expensive and less accessible metrics

In developing our model, we have planned to develop an optimal model that evaluates all assessed parameters across all modalities. In a secondary exploratory model, we can then weight parameters by their accessibility/cost during model development in order to obtain an implementation-ready model that contains accessible parameters and balances cost versus accuracy to promote practical use in non-tertiary centres. As an example, a difficult to obtain predictive imaging parameter may potentially be substituted by a quantitative sensory, psychological or omic parameter, or by a combination of those parameters based on their strong correlation with the imaging parameter. However, at this stage, there are no known prognostic markers for treatment response in adolescents with MSK pain. Even if MRI remains too costly to serve as an MSK pain prognostic marker in clinical practice, it does not preclude using MRI to discover potential prognostic markers and therapeutic targets. Additionally, an integrated model containing imaging parameters next to QST, OMIC and psychological parameters may reveal signatures that are convergent and as such particularly plausible. Plausibility weighs high on the list of criteria to promote further refinement and validation of a predictive signature. MRI is currently the most promising tool to identify pain-related prognostic markers in light of our preliminary data and data of others in the field (used to successfully identify markers for acute pain),[102] the transition from subacute to chronic pain,[38] placebo response in chronic pain,[103] fibromyalgia[4] and in other disease groups such as depression.[5] Its inclusion in our experimental approach seems therefore well justified.

Sample size justification and power analysis

For analysis of the primary study outcome where we expect 40%–60% of patients to be persistent (vs recovered), we estimated the sample size required to identify moderate effect sizes of at least 0.52 (Cohen's w) for binary prognostic markers and at least 0.27 (Cohen's d) for standard normal continuous prognostic markers,

assuming 50% as our event rate, an alpha of 0.05% and 80% power. Under these assumptions, a sample size of 175 patients is required for the signature discovery phase.

With multiple markers, we are performing multiple testing. In order to ensure the family-wise type I error remains at the nominal 5% and we maintain power at 80%, we will employ a correction for multiple testing that increases the minimum effect size needed to detect significant prognostic markers. Assuming the conservative Bonferroni correction and taking the example of 100 markers, we would detect all markers with effects 1.543 times those calculate above. For continuous markers, this is 0.35 (0.42 for n=175) and for binary 0.69 (0.80 for n=175). Both are medium to large effect sizes, and so even with 100 predictors, we are well placed under the assumptions above for our sample size to find multiple prognostic markers. Furthermore, when using machine learning for each dataset, we expect to have greater power to detect sets of markers due to the regularisation imposed by EN. For the overall integrated prognostic modelling of which 50% are persistent, assuming an alpha of 0.05% and 80% power, any model achieving an Area Under the Curve (AUC) of at least 0.8 will be demonstrated as statistically significantly better than our defined threshold for success of AUC=0.7.

In the validation of the prognostic model phase in a second independent prospectively collected patient cohort, assuming 50% of patients are persistent (vs recovered), an alpha of 0.05% and 80% power for testing the observed AUC exceeds 0.7, we will require 100 patients and an observed AUC of 0.83. This ensures we maintain the minimum threshold set in the discovery phase of the study, and we observed a slightly higher effect size to ensure the model has generalised well. This sample size was set as 80% of our target recruitment of 125 for the validation phase, which if achieved, will improve power for the estimate of 0.83%–87% power.

Ethics and dissemination

The study complies with the NIH Policy on the use of single IRB (sIRB) for multisite research, with CCHMC Review Board as the reviewing IRB. Stanford's IRB is a relying IRB within the sIRB. As foreign institutions, the University of Toronto (UoT) and The Hospital for Sick Children (SickKids) are overseen by their respective ethics boards for IRB approval rather than within the sIRB. Research procedures are conducted according to good clinical practice and monitored by the lead investigator at each site, as well as the protocol director Dr Laura Simons.

Patient and public involvement

Patient and public were not involved in the design of the study.

Data sharing

We are committed to open-access publication, so that patients, clinicians and scientists can have access to the study data and the signature(s) derived. After findings have been published, we will upload a limited data set for sharing with other investigators on applicable repositories. Potential repositories include: OpenPain, OpenNeuro, Open Science Framework, flowrepository and ImmPort. This will also include a data dictionary to facilitate and provide code used to create analytic files for primary and secondary findings so that reporting of certain variables is consistent and fully transparent. Moreover, there will be a publication charter and committee in place to review requests for data access and proposals so that we grant access to investigators to ensure scientific integrity of studies conducted using these data (and to avoid overlap). We will also present our findings at local, national and international conferences. Furthermore, all sites (Stanford, SickKids and CCHMC) have dedicated media relations offices, who help disseminate the research findings to the media.

DISCUSSION

The SPRINT study represents a multi-institutional effort from Stanford University School of Medicine, University of Toronto/Hospital for Sick Children and Cincinnati Children's that is leveraging a standardised specimen collection, processing, storage and distribution system via Stanford Biobank to aggregate the sample inventory with clinical annotations for an accessible, virtual biobank. Evidence to date informed the selection of novel candidates for neuroimaging, immune, quantitative sensory and psychological markers, and we are leveraging machine learning approaches to extract reliable and prognostic multivariate signatures from a large and complex data set. This pipeline will provide the basis for the development of robust algorithms to set long-term benchmarks for the entire field. We will probe whether and to what extent each data domain contributes to an integrated model predicting the course of MSK pain and whether the number of model parameters can be reduced to a set of parameters that can be practically implemented in clinical decision making and the enrichment of clinical trials studying the condition.

We foresee a number of clinical benefits that can result from this work. A signature robustly predicting the clinical course of paediatric chronic MSK pain will facilitate risk-stratifying patients, which will enable clinicians to educate their patients and families regarding their prognosis. Risk stratification enables a precision medicine approach where individual patients can be assigned to distinct care pathways differing in treatment selection, timing and duration. For example, only a portion of patients with poor predicted recovery trajectories may require resource-intense and demanding multidisciplinary treatment approaches. A predictive model will also provide new insights into biological and behavioural processes that drive the clinical course of MSK pain, which may lead to novel interventions, particularly profiting those who remain refractory to current approaches.

Finally, our work will generate data-driven hypotheses that can be tested to further our understanding of the mechanisms and patient vulnerabilities that underlay the complex pathogenesis and clinical course of paediatric chronic MSK pain. Such understanding will help mitigate the risk of long-term chronic pain in adolescence during a sensitive period of human development.

Reduction of model parameter to a few biological and/or clinical features that can readily be assessed is critical for the implementation of such a model as a predictive tool in clinical practice. As such, the current approach simultaneously examining important biological, imaging, sensory, psychometric and clinical domains offers distinct advantages. For example, we may detect that redundancies echoed in different domains can be exploited. More specifically, a particular prognostic parameter that is difficult to assess in daily clinical practice such as a neuroimaging correlate (eg, nucleus accumbens structure) could be substituted with a redundant but easier to assess parameter (eg, self-report of motivation/readiness to change). Importantly, if a few biological features are critical in a reduced model, such features can be measured by clinical laboratories. For example, select prognostic immune features can be assessed with aid of widely available flow cytometry technologies. The context-of-use has to be carefully considered when deriving prognostic signatures. Our study is tailored towards the prediction of the clinical course of MSK pain in adolescence to enable personalised treatment pathways from those with poor prognosis to resource intense, demanding interventions and for those with a positive prognosis to educational and self-directed inteventions.

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