American Journal of Medical Genetics Part A

WILEY

AMERICAN JOURNAL OF medical genetics PART A

ORIGINAL ARTICLE

International Expert Opinion on Standard of Care for Patients With Schinzel-Giedion Syndrome: A Modified Delphi Study

Jessica Duis[1,2,3] | Laura Agresta[4] | William E. Bennett Jr[5] | Henry Chambers[6,7] | Antonia Clarke[8] | Charlie Fairhurst[9] | Julie Hoover-Fong[10] | Feilim Murphy[11] | Garey Noritz[12] | Scott Schwantes[13] | Michael Shreve[14] | Kabelo Thusang[15] | Darcy Weidemann[16,17] | Rebecca Beale[18] | Aditi Mehta[18] | Andrew Wilhelmsen[19] | Nuala Summerfield[3]

[1]Rare Disease Doc, Aurora, Colorado, USA | [2]Children's Hospital Colorado, University of Colorado, Aurora, Colorado, USA | [3]The Schinzel-Giedion Syndrome Foundation, West Sussex, UK | [4]Department of Pediatrics and Human Development, Michigan State University, East Lansing, Michigan, USA | [5]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana, USA | [6]Department of Orthopedic Surgery, University of California San Diego, San Diego, California, USA | [7]Southern Family Center for Cerebral Palsy, Rady Children's Hospital-San Deigo, San Diego, California, USA | [8]Department of Pediatric Neurology, St George's University Hospitals NHS Foundation Trust, London, UK | [9]Department of Children's Neurosciences, Evelina London Children's Hospital, London, UK | [10]Department of Genetic Medicine, Greenberg Center for Skeletal Dysplasias, Johns Hopkins University, Baltimore, Maryland, USA | [11]Department of Pediatric Urology, St George's University Hospitals NHS Foundation Trust, London, UK | [12]Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University, Columbus, Ohio, USA | [13]Department of Pain, Palliative Care, and Integrative Medicine, Children's Minnesota, Minneapolis, Minnesota, USA | [14]Children's Respiratory and Critical Care Specialists, Minneapolis and St. Paul, Minnesota, USA | [15]Department of Neurology and Ophthalmology, Michigan State University, East Lansing, Michigan, USA | [16]Department of Pediatrics, Division of Nephrology, Children's Mercy Kansas City, Kansas, Missouri, USA | [17]University of Missouri-Kansas City School of Medicine, Kansas, Missouri, USA | [18]Costello Medical, London, UK | [19]Costello Medical, Manchester, UK

Correspondence: Jessica Duis (jessica.duis@sgsfoundation.org)

Received: 11 November 2024 | **Revised:** 20 January 2025 | **Accepted:** 22 January 2025

Funding: The authors received no specific funding for this work.

Keywords: Delphi technique | recommendations | Schinzel-Giedion syndrome | standard of care

ABSTRACT

Schinzel-Giedion Syndrome (SGS) is an ultra-rare, multisystem, genetic developmental disorder caused by gain-of-function pathogenic variants in the *SETBP1* gene. No standard of care (SoC) recommendations currently exist. To assess expert opinion on SoC for individuals with SGS using a modified Delphi method. A multidisciplinary panel of 21 experts from the USA and Europe was assembled. Experts responded to a two-round questionnaire, with a subgroup participating in a virtual workshop, through which recommendations pertaining to the diagnosis, monitoring, treatment, and management of SGS were iteratively developed. Consensus was defined as ≥ 70% of respondents demonstrating agreement/disagreement with 6-point Likert scale questions, or ≥ 70% of respondents selecting a given multiple-choice question option. Overall, 81/94 statements achieved consensus. Experts agreed that the recommendations should be considered applicable to any individual with confirmed SGS or an indicative phenotype and any *SETBP1* gain-of-function mutation. Key considerations included early and sustained involvement of a multidisciplinary team, routine monitoring for common tumors, neurologic, renal, genitourinary, pulmonary, musculoskeletal and gastrointestinal manifestations/complications, and facilitation of shared decision-making processes. These recommendations should help guide clinicians and families/caregivers in care decisions to enhance quality and duration of life for individuals with SGS and facilitate shared decision-making.

1 | Introduction

A brief plain language summary of this publication is available in the Supporting Information Data S1. Schinzel-Giedion Syndrome (SGS; OMIM number: 269150) is an ultra-rare developmental disorder. Approximately 80 cases have been reported worldwide within the medical literature to date; however, the exact prevalence is unknown (Leone et al. 2020; Liu et al. 2018). The clinical presentation of affected individuals has been variously described and classified, with a modest level of agreement surrounding the definition of so-called 'classic' SGS. Amongst other pronounced traits, classic SGS is commonly characterized by distinct dysmorphic facial features (including a prominent forehead, bitemporal narrowing, midface retrusion, hypertelorism, infraorbital crease, short nose with upturned nasal tip, and low-set, abnormally formed ears). Individuals also present with neurological problems (including severe developmental delay, epilepsy and hearing and/or vision impairment thought to be of cerebral origin), skeletal abnormalities (including sclerotic base of the skull, wide supraoccipital-exoccipital synchondroses, broad ribs, increased cortical density or thickness, hypoplastic distal phalanges, and talipes equinovarus), and hydronephrosis (Acuna-Hidalgo et al. 2017; Al-Mudaffer et al. 2008; Lehman et al. 2008; Schinzel and Giedion 1978). Furthermore, affected individuals have an increased pediatric cancer risk, which includes risk of sacrococcygeal teratoma and hepatoblastoma (Robin et al. 1993).

SGS arises from de novo germline gain-of-function pathogenic variants in a hotspot of the *SETBP1* gene, which encodes for SET Binding Protein 1, a protein that binds the SET nuclear oncogene and is involved in DNA replication (Acuna-Hidalgo et al. 2017; Hoischen et al. 2010; National Center for Biotechnology Information 2004; Morgan et al. 2021). Pathogenic variants most commonly occur within the *SETBP1* degron. As degrons are specific amino acid sequences that signal for a protein's degradation (Acuna-Hidalgo et al. 2017), these variants disrupt normal protein degradation and result in toxic accumulation of SET Binding Protein 1, in turn altering gene expression regulation and disrupting the normal development of multiple organ systems (Huisman and Huisman 2023; Piazza et al. 2018). In some cases, *SETBP1* variants outside of the degron have been reported, typically resulting in atypical cases with milder phenotypes (Acuna-Hidalgo et al. 2017; Carvalho et al. 2015; Yang et al. 2022). Although the physiological role of *SETBP1* has yet to be fully elucidated, the gene has also been implicated in the development of cancer through somatic mutations (Acuna-Hidalgo et al. 2017; Anyanwu et al. 2017; Hoischen et al. 2010). Specifically, studies show that somatic *SETBP1* mutations are associated with chronic myeloid leukemia, as these mutations help myeloid cells proliferate more aggressively (Acuna-Hidalgo et al. 2017; Makishima et al. 2013; Piazza et al. 2013).

Historically, most individuals with SGS have not survived past childhood (Acuna-Hidalgo et al. 2017). Commonly reported causes of death in early infancy include pneumonia, tumors, lung hypoplasia, intractable seizures, feeding difficulties, and sudden cardiac arrest (Acuna-Hidalgo et al. 2017). Whilst SGS is a life-limiting condition, if the family/caregiver pursue multidisciplinary complex care support, many of the symptoms and associated complications of the condition can be managed on a long-term basis, which may increase the quality and duration of life in these individuals. At present, however, no standard of care (SoC) recommendations exist for SGS (Duis and van Bon 2024), and little primary literature exists to guide its management. As an ultra-rare condition, physicians are unlikely to have previously diagnosed and/or treated an individual with SGS. The absence of such recommendations presents the treating physician with a lack of resources with which to inform their decisions and impacts the ability of families and caregivers to identify and request relevant healthcare services, limiting their ability to meaningfully engage in shared decision-making.

Thus, there exists an unmet need that requires expert SoC recommendations for SGS, to support physicians and healthcare teams, families/caregivers, and patients themselves. The Delphi technique provides a means to explore care considerations by using an iterative process to gather consensus from a group of experts, providing a systematic, robust, and reproducible methodology (Hsu and Sandford 2007). The Delphi methodology has four key characteristics: anonymity between participants, iteration incorporating structured group feedback, statistical aggregation of group response, and expert input. The Delphi technique is appropriate to use when there is a lack of agreement, evidence, or incomplete knowledge (Trevelyan and Robinson 2015); this is particularly the case for rare diseases, as data from randomized controlled trials are often limited. Accordingly, the Delphi technique has previously been used to develop clinical guidelines for managing specific rare diseases (St Louis et al. 2024; Stelten et al. 2021; Stepien et al. 2023) and by the American College of Medical Genetics and Genomics Therapeutics Committee to generate a clinical practice resource for mucopolysaccharidosis type II (McBride, Berry, and Braverman 2020). The methodology has previously been described in detail (Linstone and Turoff 1975).

Here, we establish consensus on global SoC recommendations pertaining to the diagnosis, monitoring, and management of individuals with SGS using a modified Delphi panel, encompassing questionnaires and a virtual workshop, conducted between March 2023 and January 2024.

2 | Materials and Methods

2.1 | Steering Committee

A steering committee was established to develop key themes and questions to be explored across the Delphi process, as well as to inform the phrasing of questions, review results, and support the development of each subsequent round. The steering committee comprised the founder of The SGS Foundation—an expert through lived experience (NS), and a clinical geneticist and special care pediatrician with significant experience of caring for individuals with SGS (JD). To avoid potential bias, the steering committee did not complete the questionnaires or actively participate in the workshop.

2.2 | Delphi Panelists

Although no clear rule exists regarding the requisite number of panel experts and their selection criteria in a Delphi study, it has been recommended to engage at least 10 experts (Lee,

Kim, and Han 2020). As Delphi studies rely on expert opinion, the appropriate composition of the expert panel, in terms of balance across knowledge, experience and expertise, is paramount to obtaining quality data (Lee, Kim, and Han 2020). Thus, emphasis was placed on gaining wide representation across healthcare settings and specialties in the USA and Europe. A total of 22 experts provided their consent to participate, and 21 subsequently participated in at least one round. Specifically, 21 experts participated in Round 1, with 19 experts completing the round, and 18 experts participated in and completed Round 2.

Candidate experts were identified through The SGS Foundation and invited via email to participate in the study (convenience sampling). The main criteria for the invitation of experts were professional knowledge and experience within the management of complex care conditions, including experience treating at least one individual with SGS.

Participants comprised 20 experts from the United States of America ($n=15$), United Kingdom ($n=4$) and the Netherlands ($n=1$). Experts had, on average, ~15 years of experience working with individuals with SGS and/or similar complex neurodevelopmental/multisystem disorders.

2.3 | Study Design

2.3.1 | Modified Delphi Technique

Classical Delphi studies are typically designed to continue until consensus is achieved for all questions, however there are often diminishing returns with additional questionnaire rounds; three rounds of questionnaires is commonly enough to attain stability in responses (Linstone and Turoff 1975). For efficiency and to reduce questionnaire fatigue, this study utilized a two-round modified Delphi technique to pursue consensus on diagnostic criteria and standards of care. The modified Delphi methodology comprised two rounds of online questionnaires (utilizing a web application developed by Costello Medical that provides a platform for designing, running, and analyzing Delphi panels—the 'Costello Medical Delphi App'; all responses remained anonymous to the other participants), followed by a virtual workshop where a subgroup of participants was invited to vote on, and provide comments pertaining to, questions that had not yet achieved consensus. This subgroup was selected pragmatically, based on representation of specialties and logistical considerations. All participating experts provided written informed consent via email prior to participation. No patients were directly involved in the study, nor was patient-protected health information used; as such, ethical approval was not required.

2.3.2 | Question Types and Pre-Specified Consensus Thresholds

Questions comprised either Likert-scale, multiple-choice, or free-text responses (Table 1); the format for each question was chosen pragmatically based on the content and perceived complexity of each topic. For instance, when a number of potential treatment options were identified in the literature, these options were consolidated into a single multiple-choice question, to ensure participants did not have to respond to several Likert-scale questions on the same topic. Likert-scale question responses were classified as either disagree: 'strongly disagree', 'disagree', 'somewhat disagree', or agree: 'strongly agree', 'agree', 'somewhat agree'. For all question types and for every question asked in both questionnaires and at the virtual workshop, participants could also answer with 'insufficient expertise' or 'do not wish to answer' (providing an option for Likert-scale questions in lieu of 'neither agree nor disagree'). Although the chosen experts had experience managing patients across disciplines, this approach ensured that experts were only providing insights on topics for which they had expertise, thereby reducing the risk of inaccurate or skewed information. Furthermore, all questions contained a free-text field, allowing respondents to add additional information; free-text responses were not evaluated for consensus.

For the purpose of this modified Delphi process, consensus achievement was recognized for any question for which more than 70% of respondents choosing to answer were in agreement (if a Likert-scale or binary ['yes'/'no'] question), indicative of a Kendall's Coefficient of Concordance (W) ≥ 0.7, or any option selected by more than 70% of respondents choosing to answer the question (if a multiple-choice question). This level of agreement has been used in previous studies conducted using the Delphi technique (Stelten et al. 2021). Analysis of results was performed by AM, AW and RB, independent of the steering committee and expert panel.

2.3.3 | Rounds 1 and 2 Questionnaires

A targeted literature review (TLR) was undertaken prior to drafting the first questionnaire, to identify the body of relevant literature, including any existing recommendations or guidelines. Searches, targeting publications specifically referencing SGS or *SETBP1* gain-of-function pathogenic variants were conducted in PubMed on November 25, 2022 (Table S1). A total of 125 unique articles were identified. Eligible articles reported on patients diagnosed with any form of SGS, per clinician opinion, as well as patients with any other gain-of-function pathogenic variants (but not loss-of-function or haploinsufficiency disorder) in the *SETBP1* gene. Full eligibility criteria are reported in Table S2. A teleconference was held with the steering committee to discuss TLR findings and candidate questions. The steering committee reviewed the draft Round 1 Questionnaire prior to finalization. Round 1 comprised 23 Likert-scale, 21 free-text response, and 26 multiple-choice questions. However, one Likert-scale question was retrospectively removed as it was deemed out of scope, resulting in a total of 22 Likert-scale questions.

Questions achieving pre-specified consensus (according to question type) in Round 1 were considered to have achieved consensus and were removed. As a pragmatic filter to reduce questionnaire burden, questions achieving less than 50% agreement were considered to have failed to achieve consensus and to be unlikely to achieve consensus in the subsequent round and so were removed. Similarly, options in multiple-choice questions selected by more than 70% or less than 50% of respondents were removed for the subsequent round. Questions and options for which between 50% and less than 70% agreement/selection

TABLE 1 | Question types and consensus thresholds used in questionnaires.

Question type	Definition	Example questions	Consensus threshold	Agreement threshold for rephrasing/restating the question
6-Point Likert-scale	Assessing agreement through options from 'strongly disagree' to 'strongly agree'. 6-Point scales were used to ensure participants indicated a preference towards either agreement or disagreement.	Please indicate how strongly you agree or disagree, in cases where prenatal abnormalities are suspected, with undertaking amniocentesis as an investigative procedure during the prenatal period[a]	More than 70% participants agreeing/ disagreeing	Between 50% and less than 70% participants agreeing/disagreeing
Multiple-choice	Participants asked to select from a list of options; participants could select all presented options or none	Please select all craniofacial criteria from the list below that you believe should be included within new diagnostic criteria for classic (Type I) SGS:[b] • Prominent forehead • Midface retraction • Short, upturned nose • Large fontanelles • Hypertelorism • Dysplastic ears • Large mouth • Wide occipital synchondrosis • Sclerosis of the skull	Any given option selected by more than 70% participants	Any given option selected by between 50% and less than 70% participants
Free text	Open-ended questions at the end of each section in the Round 1 questionnaire and throughout the questionnaire to explore participants' opinions on a variety of topics. • Optional free-text field for all questions, allowing participants to provide context for their responses.	• If you have any additional comments on the questions relating to general treatment and management in individuals with SGS, please feel free to add them here[c] Please provide any suggestions and recommended medications for an epilepsy emergency plan in individuals with SGS[b] • Include any notes or justification for your response here[d]	N/A; not evaluated for consensus	N/A; not evaluated for consensus

Note: Participants could select 'Insufficient expertise' or 'Do not wish to answer' for any questions they did not feel comfortable answering; all questions contained a free-text field, allowing participants to add any additional information they wished.
Abbreviation: SGS, Schinzel-Giedion Syndrome.
[a]Example question from Round 2 questionnaire.
[b]Example question from Round 1 questionnaire.
[c]Example question from Round 1 questionnaire whereby participants could add additional details at the end of a questionnaire section.
[d]Text prompting participants to add any context they wished to their responses, in both Round 1 and 2 questionnaires.

was attained were rephrased and/or restated in Round 2, following steering committee review. Free-text responses were reviewed by the steering committee and helped to inform/refine subsequent question development; for example, in cases where responses indicated confusion with the wording. Additional questions could also be introduced in response to free-text answers received, per the steering committee's judgment. Round 2 comprised 30 Likert-scale questions and 4 multiple-choice questions.

2.3.4 | Virtual Workshop

The same question filtering rules were applied to the Round 2 questions; those achieving between 50% and less than 70% agreement/selection were rephrased and/or restated in a virtual workshop, following steering committee review. Additionally, questions deemed particularly relevant by the steering committee which fell short of the 50% threshold were discussed at the virtual workshop. All questions were clarified for the expert panel as needed. A select panel of 13 experts (a convenience sample of the total participant pool) was invited to attend a virtual workshop in which 11 final, consensus-seeking questions were posed (nine Likert-scale; two multiple-choice); nine experts ultimately attended. Any questions not achieving consensus by the end of the workshop were discussed in an open forum; in lieu of further pursuing specific recommendations, the group had the opportunity to informally agree on broader suggestions.

3 | Results

An overview of the modified Delphi process used, the number of respondents, and a summary of the consensus status at each stage is presented in Figure 1.

3.1 | Consensus on Statements

In Round 1, 86.4% (19/22) of Likert-scale questions achieved consensus, and 96.2% (25/26) of multiple-choice questions achieved consensus on at least one option. Of the 21 free-text questions, responses for eight questions were carried forward to either Round 2 or the workshop in a consensus-seeking format. Thirty-four questions were subsequently asked in Round 2; 86.7% (26/30) of Likert-scale questions achieved consensus, and 100% (4/4) of multiple-choice questions achieved consensus on at least one option. Of 11 questions carried forward to the workshop, a formal vote was not undertaken for two Likert-scale questions, as experts did not feel comfortable voting for the questions in the form that they were asked. Of the remaining Likert-scale questions, 85.7% (6/7) achieved consensus. Both multiple-choice questions achieved consensus on at least one option.

The following sections briefly explain the key results in each section, and summaries of consensus-achieving statements (i.e., recommendations) are provided in Table 2 (screening and diagnosis), Table 3 (monitoring), and Table 4 (treatment and management). Full details on all consensus-achieving statements (i.e., recommendations) are available in Table 5 (screening and diagnosis), Table 6 (monitoring) and Table 7 (treatment and management). Further details on questions that did not achieve consensus across the Delphi process are reported in Table S3 (screening and diagnosis), Table S4 (monitoring) and Table S5 (treatment and management).

3.2 | Screening and Diagnosis Recommendations

Consensus was achieved on a variety of conditions that should be considered in the differential diagnosis of SGS, which are presented in Tables 2 and 5, along with initial diagnostic criteria considerations for classic and atypical SGS. Experts ultimately agreed, however, that for the purposes of standard of care recommendations, all individuals with a phenotype suggestive of SGS (Table 2) who exhibit any *SETBP1*-gain-of-function pathogenic variants (including de novo *SETBP1* gene variants of uncertain significance near the degron) should receive the same standard monitoring, treatment and management recommendations in the first instance. Thus, for this purpose, experts agreed that a single term of 'SGS' is functionally adequate to encompass the spectrum of findings present in all *SETBP1*-gain-of-function pathogenic variants and the recommendations made in this study should be considered for such patients.

In any case of suspected SGS, including in infants or toddlers with severe developmental delay/intellectual disability and/or epilepsy/epileptic encephalopathies of unknown cause, a molecular genetic diagnosis should always be sought, with *SETBP1* investigated as a gene of interest. To note, some experts indicated the importance of also considering SGS and investigating *SETBP1* in cases where infants or toddlers present with neurological problems of unknown etiology; however, these situations were not formally voted upon by the entire expert panel.

Where possible, exome or genome sequencing should be sought as the molecular test of choice to confirm a diagnosis of SGS; these methods are preferred because they allow for the potential identification of pathogenic variants in other genes, if SGS is not the correct diagnosis. In cases where prenatal abnormalities, such as craniofacial and kidney abnormalities, are present/suspected and suggestive of a neurodevelopmental disorder like SGS, amniocentesis should be undertaken, with a fetal echocardiogram performed when relevant prenatal structural anomalies are suspected. Where genetic mosaicism is suspected (e.g., in cases where the clinical presentation deviates from expectations, genetic testing of tissue excised for the patient's clinical care should be undertaken to identify possible genetic mosaicism). If testing of the first choice of tissue is not revealing (e.g., tumor tissue), genetic testing of a skin biopsy should instead be undertaken to look for mosaicism.

3.3 | Monitoring Recommendations

A summary of consensus-achieving statements relating to the monitoring of individuals with SGS is provided in Table 3; the full list of consensus-achieving statements is provided in

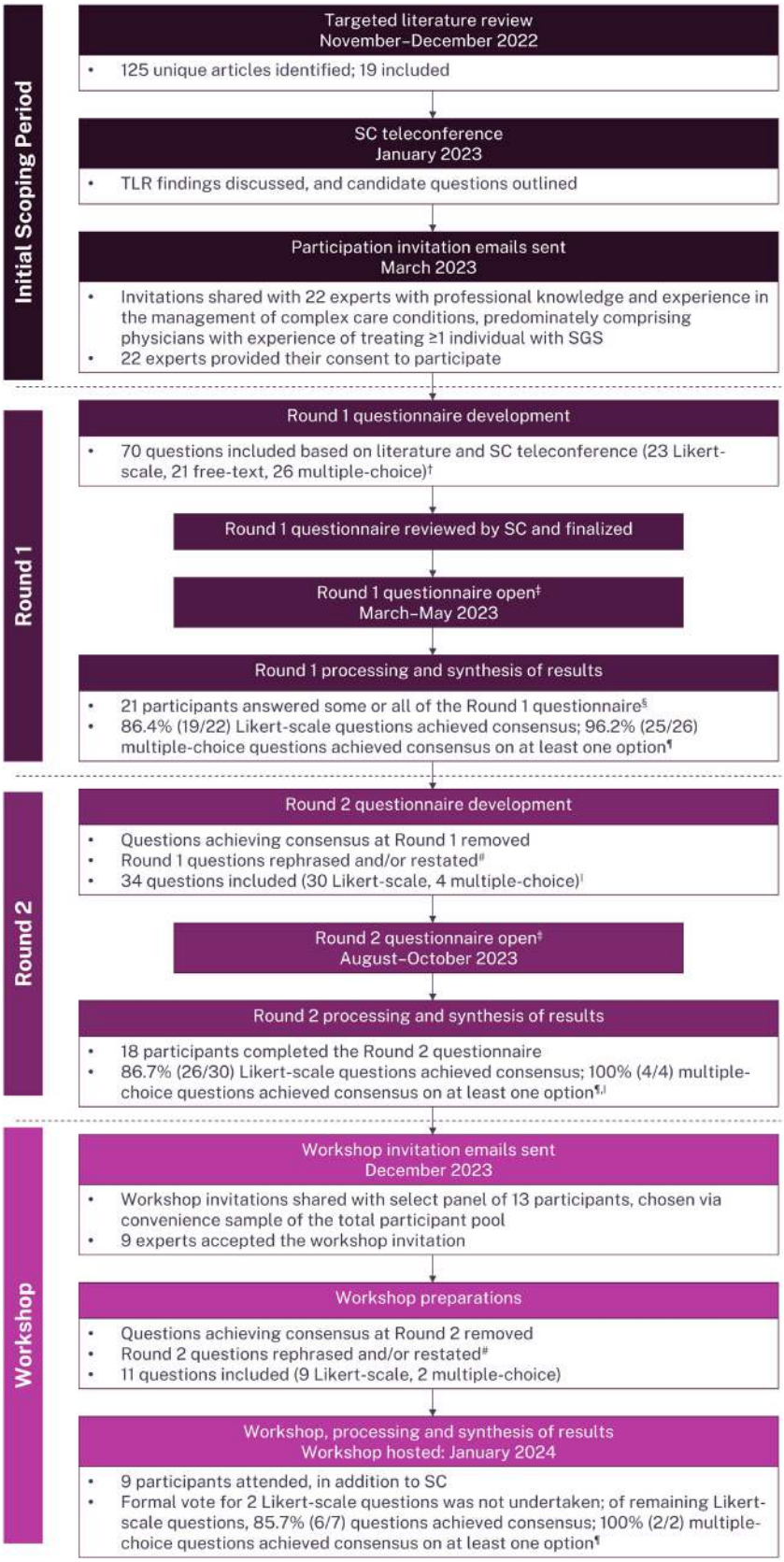

FIGURE 1 | Legend on next page.

Table 6. The following recommendations form a basis for standard monitoring procedures and apply to all individuals with confirmed or suspected SGS. The frequency of such monitoring procedures should be in accordance with standard/local guidelines, adjusted according to the individual's unique presentation and aligned with the individual's and/or family's goals of care.

3.3.1 | Oncology

The expert committee agreed that all patients with SGS should be offered regular surveillance for all SGS-associated tumors, including germ cell tumors/cancers, Wilms tumors, hepatoblastomas, and primary brain and central nervous system tumors/cancers. Routine serial measurement of germ cell tumor markers alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (β-hCG) are recommended for monitoring purposes. Additionally, there was consensus that regular pelvic ultrasound scans should be undertaken in early infancy to monitor for sacrococcygeal teratomas (Table 6).

3.3.2 | Cardiology

Echocardiograms should be performed, first in early infancy to identify congenital cardiac defects (e.g., atrial septal defect), and then routinely for cardiac monitoring if clinically indicated (Table 6).

3.3.3 | Neurology

For the monitoring of neurological complications, including associated seizures and developmental delay, routine head circumference measurements to monitor hydrocephalus and microcephaly should be standardly undertaken. Additional consensus-achieving monitoring recommendations for brain malformations and hydrocephalus are reported in Table 6.

3.3.4 | Nephrology and Urology

Participants agreed that symptomatic monitoring for urinary tract infections (UTIs) and kidney and bladder ultrasounds to monitor overall kidney and bladder health should occur routinely. Routine ultrasonography is recommended to monitor for congenital anomalies of the kidneys and urinary tract. Kidney function should be assessed using serum creatinine measurements to determine estimated glomerular filtration rate (Table 6).

3.3.5 | Gastroenterology and Feeding

An upper gastrointestinal (GI) series should be conducted to assess for anatomic gastrointestinal anomalies. Additionally, measurement of skeletal growth and body mass, as well as evaluation of nutritional status, should be standardly undertaken in individuals with SGS (Table 6).

3.3.6 | Otolaryngology and Dentistry

Assessments of oral intake safety, saliva production/control, swallowing studies to monitor dysphagia, and routine oral hygiene/dental checks should be performed (Table 6).

3.3.7 | Orthopedics

Experts agreed orthopedic monitoring should routinely include occupational and physical therapy mobility assessments, as well as assessment of limb/foot contracture. Whilst consensus was not achieved for the routine performance of skeletal surveys for all individuals with SGS, participants informally agreed in the workshop that such decisions should be made by the assigned specialist and in accordance with local guidelines for the monitoring of conditions with broadly similar considerations, such as cerebral palsy (Table 6).

3.3.8 | Vision and Hearing

Routine ophthalmological and audiological assessments should be performed as standard, including functional vision and hearing tests for the assessment and monitoring of cerebral visual impairment. However, experts agreed that MRIs of the brain should not be routinely undertaken for this purpose (Table 6).

3.3.9 | Palliative, Hospice and Community Care

Experts agreed that families/caregivers should, as standard, receive a needs assessment for support outside of the clinic, including options for palliative/hospice support, community/private nursing, and social workers/case managers (Table 6).

3.3.10 | Pulmonology

Owing to the high prevalence of aspiration in individuals with SGS, evaluation for evidence of aspiration and respiratory

FIGURE 1 | Flow diagram of the modified Delphi methodology. [†]One Likert-scale question was retrospectively removed as it was deemed out of scope, resulting in a total of 22 Likert-scale questions; [‡]The Round 1 and 2 questionnaires were distributed through an in-house Delphi app; invitations to complete the questionnaires were shared as a web link via email; [§]1 participant answered 43/70 questions; 1 participant answered 10/70 questions; [¶]Consensus for Likert-scale questions: More than 70% participants agreeing/disagreeing; consensus for multiple-choice questions: Any given option selected by more than 70% participants; [#]Likert-scale questions were rephrased/restated if between 50% and less than 70% agreement/disagreement was attained; multiple-choice questions were rephrased/restated if between 50% and less than 70% agreement/disagreement was attained for any given option; [‖]One Likert-scale question was erroneously restated in Round 2, but the outcome was unchanged. SC, steering committee; SGS, Schinzel-Giedion Syndrome; TLR, targeted literature review.

TABLE 2 | Summary of diagnostic considerations, screening recommendations, and diagnostic procedure recommendations for SGS.

Diagnostic considerations			
If individuals present with the following features and/or a *SETBP1* gain-of-function mutation, the below investigative procedures should be undertaken to obtain a diagnosis of SGS, and the following monitoring, treatment and management recommendations should be considered for any such patients.			
Key features of classic (Type 1) SGS	• Any gain-of-function pathogenic variants in the *SETBP1* gene • Developmental delay	• Prominent forehead • Midface retraction • Large fontanelles	• Hydronephrosis • Hypertrichosis
	• Individuals with a short, up-turned nose and/or ocular hypertelorism in conjunction with the above criteria should be considered as having a form of SGS and thus treated and monitored with (in the first instance) the same foundational recommendations as those with a confirmed genetic diagnosis		
Distinguishing features of atypical SGS	• Confirmed pathogenic variant in the *SETBP1* gene	• Milder phenotype that may include craniofacial findings	• Developmental delay
Conditions/syndromes to be considered within the differential diagnosis	• Mucolipidosis II alpha/beta (I-cell disease) • Mucopolysaccharidoses	• Coffin-Siris Syndrome • DOORS Syndrome	• Cornelia de Lange Syndrome • Osteodystrophy (osteodystrophy presenting with coarse facies might be particularly relevant in the differential diagnosis of individuals with SGS)[a]
Screening and diagnostic procedure recommendations			
Investigative procedures to undertake if prenatal abnormalities are suspected	• Fetal echocardiograms	• Amniocentesis	
Preferred procedures to undertake to identify possible genetic mosaicism	• Genetic testing of excised tissue (e.g., tumor) • Genetic testing of a skin biopsy, if genetic testing of first choice of tissue is not revealing		
SETBP1 to be investigated as a gene of interest during molecular genetic diagnostic procedures for the following groups	• Those with severe developmental delay/intellectual disability of unknown cause • Those with epilepsy/epileptic encephalopathies of unknown cause		
Preferred procedures to use to obtain a molecular genetic diagnosis when SGS is suspected	• Rapid genome sequencing	• Exome sequencing	• *SETBP1* sequence analysis

Note: Where multiple recommendations are listed, they are listed in order of percentage agreement.
Abbreviations: DOORS, deafness, onychodystrophy, osteodystrophy, developmental delay and intellectual disability, and seizures; *SETBP1*, SET binding protein 1; SGS, Schinzel-Giedion Syndrome.
[a]Information presented in brackets was noted and informally agreed by experts, but not formally voted upon by the entire expert panel.

TABLE 3 | Summary of monitoring recommendations.

Applicability of recommendations			
In addition to those with a confirmed molecular diagnosis of SGS, the foundational recommendations presented below can be considered applicable to all individuals presenting with both a phenotype suggestive of SGS and a pathogenic *SETBP1* gain-of-function mutation (or variants of unknown significance) near the degron.			
Monitoring recommendations			
The following are the consensus-achieving recommendations for monitoring procedures across a spectrum of specialties; experts agree that these should form a basis for standard monitoring procedures from the outset of working with an individual with a confirmed or suspected case. However, due to the complex and multi-systemic nature of SGS, the clinician should thereafter determine the frequency of recurrence of these monitoring procedures based on the presentation of the individual as well as their own clinical judgment and applicable local guidelines.			
Oncology	Routinely monitor for: • Germ cell tumors • Hepatoblastoma • Primary brain/central nervous system tumors • Wilms tumors	• Undertake regular pelvic ultrasound scans in early infancy	• Routinely measure tumor markers
Cardiology	• Conduct echocardiograms first in early infancy to identify congenital cardiac defects and then routinely for cardiac monitoring (if clinically indicated)[a]		
Neurology	• Routinely measure head circumference to monitor hydrocephalus and microcephaly • Conduct head ultrasounds in newborns to assess hydrocephalus and brain malformations • When clinically indicated, undertake brain MRI scans to monitor for development of hydrocephalus, only as and when clinically indicated		
Nephrology and urology	• Conduct symptomatic monitoring for UTIs • Undertake bladder ultrasounds to monitor bladder health • Undertake renal ultrasounds to monitor hydronephrosis, kidney function, Monitor oral hygiene/dental and general health • Assess estimated glomerular filtration rate (GFR) using serum creatinine measurement		
Gastroenterology and feeding	• Evaluate nutritional status • Measure body mass	• Undertake upper GI series to monitor gastrointestinal abnormalities	• Measure skeletal growth
Otolaryngology and dentistry	• Monitor saliva production/control • Monitor oral hygiene/dental	• Assess oral intake safety	• Monitor dysphagia using swallowing studies
Orthopedics	• Undertake physical therapy mobility assessments • Undertake occupational therapy mobility assessments • Assess limb/foot contracture		
Vision and hearing	Undertake the following exams/assessments: • Ophthalmological assessment to assess and monitor cerebral visual impairment • Ophthalmological exams • Functional vision assessments • Audiological exams • Functional hearing assessments	• Do not use MRI to assess and monitor cerebral visual impairment	

(Continues)

TABLE 3 | (Continued)

Applicability of recommendations	
Palliative, hospice and community care	• Assess family need for support/care outside of the clinical setting • Assess the need for/scope of palliative/hospice support, social workers/case managers, and community/private nursing support
Pulmonology	• Regularly assess evidence of aspiration and respiratory insufficiency

Note: Where multiple recommendations are listed, they are listed in order of percentage agreement.
Abbreviations: GFR, glomerular filtration rate; GI, gastrointestinal; MRI, magnetic resonance imaging; *SETBP1*, SET binding protein 1; SGS, Schinzel-Giedion Syndrome; UTI, urinary tract infection.
[a]Consensus-achieving statement did not include '(if clinically indicated)'; this wording has been added to the summarized recommendations for clarity.

insufficiency should be performed if swallowing dysfunction is suspected (Table 6). Authors noted that evaluating for evidence of pneumonia or pulmonary disease specifically could additionally be undertaken (e.g., with radiography), however this was not formally voted upon by the entire expert panel.

3.4 | Treatment and Management Recommendations

Although the following recommendations serve as a basis for standardized treatment and management approaches in SGS, the recommendations should be contextualized to the clinician's setting and adapted to best meet the needs of the individual with SGS and their caregivers. A summary of the statements reaching consensus relating to the treatment and management of individuals with SGS is provided in Table 4; the full list of consensus-achieving statements is provided in Table 7.

3.4.1 | General

First and foremost, all treatment and management decisions involving the care of an individual with SGS should be made through a well-informed, shared decision-making model approach that involves the parents/caregivers. To facilitate this, parents/caregivers should be engaged and educated as much as possible. Additionally, early education of parents/caregivers (e.g., at diagnosis), with regard to what palliative care includes and how a palliative care referral might be able to support them with day-to-day care should be provided (Table 7).

3.4.2 | Specialist

As far as possible, a wide variety of healthcare professionals should be involved (at least initially) in the multidisciplinary treatment and management of individuals with SGS. Beyond primary care, experts agreed that community/private duty nurses, complex care pediatricians, dietitians, geneticists, occupational therapists, palliative care specialists, physical therapists, speech and language specialists, and multisensory impairment specialists should be involved. Organ system-specific healthcare professionals that should be involved include audiologists, cardiologists, nephrologists and urologists, neurologists, ophthalmologists, orthopedic specialists, and pulmonologists (Table 7).

During the workshop, participants informally agreed that involvement of other healthcare professionals that did not achieve consensus for routine involvement, such as gastroenterologists and oncologists, should still be considered to optimize care of individuals with SGS. To note, although early referrals to specialists are important and their involvement valued, it may not be practical to involve all specialists from the point of diagnosis. As such, the physician taking primary responsibility for the patient should be aware of the potential need for, and ask for advice early on from, the recommended specialists (Table 7).

TABLE 4 | Summary of treatment and management recommendations.

Applicability of recommendations			
In addition to those with a confirmed molecular diagnosis of SGS, the foundational recommendations presented below can be considered applicable to all individuals presenting with both a phenotype suggestive of SGS and a pathogenic *SETBP1* gain-of-function mutation (or variants of unknown significance) near the degron.			
Treatment and management recommendations			
The following are the consensus-achieving recommendations for treating and managing the different manifestations of SGS; experts agree that these should serve as a basis for standardized treatment and management approaches. However, the recommendations should be contextualized to the clinician's setting based on the presentation of the individual, their own clinical judgment and applicable local guidelines, as well as adapted to best meet the needs of the individual with SGS and their caregivers.			
Recommendations to facilitate shared decision-making	• Engage and educate parents/caregivers as much as possible • Make all treatment and management decisions through a shared decision-making model approach		
Healthcare professionals who should be routinely involved (at least initially and where possible) in treatment and management (Healthcare professionals that did not achieve consensus for routine involvement, such as gastroenterologists and oncologists, should still be considered to optimize care of individuals with SGS)[a]	• Multisensory impairment specialists • Audiologists • Ophthalmologists • Nephrologists and urologists • Physical therapists • Neurologists	• Dietitians • Cardiologists • Primary or complex care pediatricians • Geneticists • Occupational therapists	• Palliative care specialists • Pulmonologists • Community/private duty nurses • Speech and language specialists • Orthopedic specialists
Dermatology	• Make a wound care referral to treat and manage pressure sores and ulcers		
Developmental pediatrics	• Refer individual to a neurodisability specialist and an early intervention program in infancy (ages 0–3), followed by developmental pre-school • Refer individual to physical and/or occupational therapy specialists • Intensive speech and language therapy should be offered		
Endocrinology	• Consider standard pharmacological treatment strategies for hormonal regulation to manage seizures, mood changes and menstrual cycle irregularity		
Gastroenterology	• Use a feeding tube to manage aspiration, failure to thrive and gastrointestinal intolerance • Use standard pharmacological treatment, postural control and continuous slow pump feeding to manage gastroesophageal reflux and gastroparesis • Use gastrostomy tube for venting to manage bloating and gastric distension • Use standard laxative pharmacological options, as indicated, and colonic irrigation and glycerin/warm water enemas for day-to-day management of constipation • Consider jejunostomy tube feeding for continued concerns regarding aspiration and/or severe reflux in an individual with a gastrostomy tube • Consider Nissen fundoplication to manage severe reflux and associate aspiration • Consider surgical procedures for severe dysmotility • Replace nasogastric tube feeding with gastrostomy/jejunostomy tube feeding as soon as possible		

(Continues)

TABLE 4 | (Continued)

Applicability of recommendations	
Urology and nephrology	• Actively treat/manage nephrolithiasis, polycystic dysplastic kidney disease, hydronephrosis, and megacalycosis • Use nephrostomy and bladder catheterization to manage hydronephrosis recurrence • Use a deflux procedure to manage vesicoureteral reflex • Use clean intermittent catheterization to manage UTI recurrence arising from neurologic bladder and bladder atony • Use prophylactic antibiotics to manage UTI recurrence • Consider vesicostomy to manage urinary malformations/neurologic bladder
Neurology	• An emergency epilepsy plan should be put in place, with training on rescue medication administration provided to family/caregivers • Subject to geographical considerations, nasal or buccal midazolam are first-choice rescue benzodiazepines; rectal diazepam as the second-choice treatment
Oncology	• Host a multidisciplinary team meeting with parents/caregivers from the point of tumor identification to consider personalized treatment plans that factor in comorbidities
Multisensory impairment	• Provide vision therapy • If ophthalmological assessment fails to identify structural differences within the eye or if visual impairment persists despite correction with interventions such as glasses, refer individual to a cerebral visual impairment specialist for educational support[b]
Orthopedics	• Treat contracture/tight tendons with botulinum toxin as needed • Use positioning devices, casting or splinting, or surgical intervention to manage scoliosis • Use orthotics or surgical intervention to manage club feet/talipes as needed • Use positioning devices, casting or splinting, or surgical intervention to manage hip dislocation
Otolaryngology	• Provide dental hygiene management advice for dental caries • Treat excessive salivation with anticholinergic medications, botulinum toxin injections, or excision of salivary glands as needed
Palliative care	• Provide early education to parents/caregivers with regards to what palliative care can entail and how a palliative care referral might be able to support them with day-to-day care and support
Pulmonology	• Conduct an overnight polysomnography with full-lead EEG to rule out central and obstructive sleep apnea and hypoxic events related to physical characteristics of SGS • Prescribe anticholinergic drugs to manage aspiration of saliva as needed • Manage frequent infections with chest physiotherapy as needed • Manage accumulation of secretions in the airways by aggressive pulmonary hygiene as needed, or by oral suction with a suction catheter or Yankauer suction tip • Manage central sleep apnea by use of supplemental oxygen or positive airway pressure therapy as needed • Use proton pump inhibitors to manage recurrent pneumonia resulting from gastro-esophageal reflux • The approach used for the prevention, treatment, and management of serious respiratory infections for individuals with SGS should align with that used for the general population (in the first instance)

Note: Where multiple recommendations are listed, they are listed in order of percentage agreement.
Abbreviations: EEG, electroencephalogram; SGS, Schinzel-Giedion Syndrome; UTI, urinary tract infection.
[a]Information presented in brackets was noted by experts and informally agreed, but not formally voted upon by the entire expert panel.
[b]'Cortical' was changed to 'cerebral' upon writing the manuscript.

TABLE 5 | Consensus-achieving statements relating to the screening and diagnosis of individuals with SGS.

Question type	Question/Statement	Percentage agreement	Responses included in analysis, *n*
Likert-scale	Mucopolysaccharidoses (e.g., Hurler Syndrome and Hunter syndrome) should be included in the differential diagnosis of SGS	87	15
Likert-scale	Mucolipidosis II alpha/beta (I-cell disease) should be included in the differential diagnosis of SGS	100	12
Likert-scale	Coffin-Siris Syndrome should be included in the differential diagnosis of SGS	85	13
Likert-scale	DOORS (deafness, onychodystrophy, osteodystrophy, developmental delay and intellectual disability, and seizures) Syndrome should be included in the differential diagnosis of SGS	82	11
Likert-scale	Cornelia De Lange Syndrome should be included in the differential diagnosis of SGS	80	15
Multiple-choice	A prominent forehead should be included within new diagnostic criteria for classic (Type I) SGS	82	11
Multiple-choice	Midface retraction should be included within new diagnostic criteria for classic (Type I) SGS	82	11
Multiple-choice	Developmental delay should be included within new diagnostic criteria for classic (Type I) SGS	93	14
Multiple-choice	Hydronephrosis should be included within new diagnostic criteria for classic (Type I) SGS	79	14
Multiple-choice	A milder phenotype that may include craniofacial findings should be included within new diagnostic criteria for atypical SGS	80	10
Multiple-choice	Developmental delay should be included within new diagnostic criteria for atypical SGS	70	10
Multiple-choice	A confirmed pathogenic variant in the *SETBP1* gene should be included within new diagnostic criteria for atypical SGS	90	10
Likert-scale	When SGS is suspected, a molecular genetic diagnosis should always be sought	89	18
Multiple-choice	In infants/toddlers (aged 0–3) with severe developmental delay/intellectual disability of unknown cause, *SETBP1* should be investigated as a gene of interest during molecular genetic diagnostic procedures	100	15
Multiple-choice	In infants/toddlers (aged 0–3) with epilepsy/epileptic encephalopathies of unknown cause, *SETBP1* should be investigated as a gene of interest during molecular genetic diagnostic procedures	100	13
Multiple-choice	In children (aged 3+) with epilepsy/epileptic encephalopathies of unknown cause, *SETBP1* should be investigated as a gene of interest during molecular genetic diagnostic procedures	77	13
Multiple-choice	For individuals with suspected SGS, whole exome sequencing or *SETBP1* sequence analysis should be undertaken to confirm the diagnosis	77	13
Multiple-choice	Genetic testing of excised tissue (e.g., tumor) should be undertaken to identify possible genetic mosaicism in individuals with SGS	86	7

(Continues)

TABLE 5 | (Continued)

Question type	Question/Statement	Percentage agreement	Responses included in analysis, *n*
Likert-scale	In cases where prenatal abnormalities are suspected, amniocentesis should be undertaken as an investigative procedure during the prenatal period (methods beyond amniocentesis could be considered, as anomalies potentially observed prenatally may not be specific to SGS)[a]	87	15
Likert-scale	Osteodystrophy should be included in the differential diagnosis of SGS (osteodystrophy presenting with coarse facies might be particularly relevant in the differential diagnosis of individuals with SGS)[a]	77	13
Likert-scale	Large fontanelles should be included within new diagnostic criteria for classic (Type I) SGS	80	10
Likert-scale	Hypertrichosis should be included as a criterion within revised diagnostic criteria for classic (Type I) SGS	77	13
Likert-scale	Any gain-of-function pathogenic variants in the *SETBP1* gene should be included as a criterion within revised diagnostic criteria for classic (Type I) SGS, for the purpose of providing standard of care guidelines[b]	100	10
Likert-scale	For the purpose of providing standard of care guidelines, individuals with a phenotype suggestive of SGS who exhibit a de novo *SETBP1* variant of uncertain significance that is near the degron, should receive the same standard monitoring, treatment and management recommendations as those individuals with (Type I) SGS	100	12
Likert-scale	For the purpose of providing standard of care guidelines, a single term of 'SGS' is functionally adequate to encompass the spectrum of findings present in all *SETBP1*-gain-of-function pathogenic variants[b]	90	10
Likert-scale	*SETBP1* should be investigated as a gene of interest during molecular genetic diagnostic procedures in children (aged 3+) with severe developmental delay/ intellectual disability of unknown cause	93	14
Likert-scale	Rapid genome sequencing should be undertaken as a molecular diagnostic procedure for suspected cases of SGS	93	15
Likert-scale	A fetal echocardiogram should be undertaken during the prenatal period in cases where relevant prenatal structural anomalies are suspected	100	7
Multiple-choice	For the purpose of providing standard of care recommendations, individuals presenting with a short, up-turned nose and/or ocular hypertelorism in conjunction with the aforementioned consensus-achieving criteria, should be considered as having a form of SGS and thus treated and monitored with (in the first instance) the recommendations arising from this Delphi process	75	4
Likert-scale	Provided genetic testing of your first choice of tissue is not revealing, genetic testing of a skin biopsy should be undertaken as an investigative procedure to identify possible genetic mosaicism in individuals with SGS	80	5

Note: Pink signifies statement achieved consensus in Round 1, blue signifies statement achieved consensus in Round 2, and yellow signifies statement achieved consensus in the virtual workshop.
Abbreviations: SGS, Schinzel-Giedion Syndrome.
[a]Information presented in brackets was noted by experts and informally agreed, but not formally voted upon by the entire expert panel.
[b]Mutation' was updated to 'pathogenic variant' upon writing the manuscript, to better reflect the nature of the gain-of-function mutations.

TABLE 6 | Consensus-achieving statements relating to the monitoring of individuals with SGS.

Question type	Question/Statement	Percentage agreement	Responses included in analysis, *n*
Oncology			
Likert-scale	Routine monitoring for germ cell tumors/cancers (such as sacrococcygeal teratoma) should be standardly undertaken in individuals with SGS	100	5
Likert-scale	Routine monitoring for Wilms tumors should be standardly undertaken in individuals with SGS	100	5
Likert-scale	Routine monitoring for hepatoblastoma should be standardly undertaken in individuals with SGS	100	5
Likert-scale	Routine monitoring for primary brain and central nervous system tumors/cancers (e.g., ependymoma) should be standardly undertaken in individuals with SGS	100	5
Likert-scale	Regular pelvic and spinal ultrasound scans should be performed in early infancy in individuals with SGS to monitor for tumors	100	5
Likert-scale	Routine measurement of tumor markers, such as alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (β-hCG), should be undertaken in individuals with SGS	80	5
Likert-scale	Regular pelvic ultrasound scans should be standardly undertaken in early infancy in individuals with SGS to monitor for sacrococcygeal teratomas	100	14
Cardiology			
Likert-scale	An echocardiogram should be performed first in early infancy to identify congenital cardiac defects (e.g., atrial septal defect) and then routinely for cardiac monitoring, in individuals with SGS	93	15
Neurology			
Multiple-choice	Routine head circumference measurements to monitor hydrocephalus should be standardly undertaken in individuals with SGS	100	13
Multiple-choice	Routine head circumference measurements to monitor microcephaly should be standardly undertaken in individuals with SGS	85	13
Multiple-choice	Head ultrasound in new-borns to assess hydrocephalus and brain malformations should be standardly undertaken in individuals with SGS	85	13
Multiple-choice	Brain MRI scans to monitor for the development of hydrocephalus (only as and when clinically indicated) should be standardly undertaken in individuals with SGS	77	13
Nephrology and urology			
Multiple-choice	Symptomatic monitoring for UTIs should be standardly undertaken in individuals with SGS	100	10
Multiple-choice	Bladder ultrasound to monitor bladder health should be standardly undertaken in individuals with SGS	90	10
Multiple-choice	Renal ultrasound to monitor hydronephrosis should be standardly undertaken in individuals with SGS	82	11
Multiple-choice	Renal ultrasound to monitor kidney function and general health should be standardly undertaken in individuals with SGS	82	11

(Continues)

TABLE 6 | (Continued)

Question type	Question/Statement	Percentage agreement	Responses included in analysis, *n*
Multiple-choice	Estimated glomerular filtration rate (GFR) assessment using serum creatinine measurement should be standardly undertaken in individuals with SGS	73	11
Gastroenterology and feeding			
Multiple-choice	Upper GI series to monitor gastrointestinal abnormalities should be standardly undertaken in individuals with SGS	83	12
Multiple-choice	Measurement of skeletal growth should be standardly undertaken in individuals with SGS	73	15
Multiple-choice	Measurement of body mass should be standardly undertaken in individuals with SGS	87	15
Multiple-choice	Evaluation of nutritional status should be standardly undertaken in individuals with SGS	93	15
Otolaryngology and dentistry			
Multiple-choice	Assessment of oral intake safety should be standardly undertaken in individuals with SGS	88	16
Multiple-choice	A swallowing study to monitor dysphagia should be standardly undertaken in individuals with SGS	75	16
Multiple-choice	Oral hygiene/dental monitoring should be standardly undertaken in individuals with SGS	100	16
Likert-scale	Monitoring of saliva production/control should be standardly undertaken in individuals with SGS	100	12
Orthopedics			
Multiple-choice	Occupational therapy mobility assessment should be standardly undertaken in individuals with SGS	93	14
Multiple-choice	Physical therapy mobility assessment should be standardly undertaken in individuals with SGS	100	14
Multiple-choice	Assessment of limb/ft contracture should be standardly undertaken in individuals with SGS	93	14
Vision and hearing			
Multiple-choice	Ophthalmological exams should be standardly undertaken in individuals with SGS	90	10
Multiple-choice	Functional vision assessments should be standardly undertaken in individuals with SGS	90	10
Multiple-choice	Audiological exams should be standardly undertaken in individuals with SGS	80	10
Multiple-choice	Functional hearing assessments should be standardly undertaken in individuals with SGS	80	10
Likert-scale	An ophthalmological assessment should be standardly undertaken, for the assessment and monitoring of cerebral visual impairment, in individuals with SGS[a]	100	7
Likert-scale	An MRI of the brain should NOT be standardly undertaken, for the assessment and monitoring of cerebral visual impairment, in individuals with SGS	100	6

(Continues)

TABLE 6 | (Continued)

Question type	Question/Statement	Percentage agreement	Responses included in analysis, *n*
Palliative, hospice, and community care			
Multiple-choice	Assessment of family need for support/care outside of the clinical setting should be standardly undertaken to support individuals with SGS and their caregivers	94	18
Multiple-choice	Assessment of the need for/scope of palliative/hospice support should be standardly undertaken to support individuals with SGS and their caregivers	94	18
Multiple-choice	Assessment of the need for/scope of community/private nursing support should be standardly undertaken to support individuals with SGS and their caregivers	78	18
Multiple-choice	Assessment of the need for/scope of social workers/case managers should be standardly undertaken to support individuals with SGS and their caregivers	94	18
Pulmonology			
Likert-scale	Regular assessment of evidence of aspiration and respiratory insufficiency should be undertaken in individuals with SGS	87	15

Note: Pink signifies statement achieved consensus in Round 1, blue signifies statement achieved consensus in Round 2, and yellow signifies statement achieved consensus in the virtual workshop. One statement was erroneously repeated in a subsequent round, but the outcome was unchanged.
Abbreviations: AFP, alpha-fetoprotein; β-hCG, beta-human chorionic gonadotropin; GFR, glomerular filtration rate; GI, gastrointestinal; SGS, Schinzel-Giedion Syndrome; UTI, urinary tract infection.
[a]"Cortical' was changed to 'cerebral' upon writing the manuscript.

3.5 | Dermatology

Participants agreed that a wound care referral should be made for the treatment and management of pressure sores and ulcers in individuals with SGS (Table 7).

3.6 | Developmental Pediatrics

For the management of developmental delay in individuals with SGS, referral to a neurodisability, physical and/or occupational therapy specialist should be undertaken. Additional consensus-achieving recommendations are reported in Table 7.

3.7 | Endocrinology

Standard pharmacological treatment strategies for hormonal regulation should be considered to manage seizures, mood changes and menstrual cycle irregularity (Table 7).

3.8 | Gastroenterology

Consensus-achieving recommendations for the management of gastroesophageal reflux disease, gastroparesis, severe reflux and associated aspiration, constipation, dysmotility, and bloating and gastric distension are reported in Table 7. Participants agreed that feeding tubes should be used to manage aspiration, failure to thrive and gastrointestinal intolerance (e.g., gastrointestinal dysmotility). To facilitate feeding and medication administration, nasogastric tube feeding should be replaced with gastrostomy/jejunostomy tube feeding as soon as possible.

3.9 | Urology and Nephrology

Consensus-achieving recommendations for the treatment and management of urological and nephrological issues, including bladder atony, urinary tract infections, urinary malformations/neurogenic bladder, vesicoureteral reflux, and hydronephrosis, are reported in Table 7.

3.10 | Neurology

Rectal diazepam and/or midazolam (nasal or buccal) are standardly recommended medications for an epilepsy emergency plan for individuals with SGS; nasal or buccal midazolam are first-choice rescue benzodiazepines, with rectal diazepam as the second-choice rescue benzodiazepine. Although not formally voted upon, experts agreed that a plan for emergency administration should be in place, and training provided on how to administer these medications under rescue conditions. Although medication use may vary based on the geography and age of the patient, participants noted that a rescue benzodiazepine should be available for all individuals with SGS (Table 7). Within the USA, current SoC for seizure rescue involves prescription of rectal diazepam for all ages, nasal diazepam for individuals aged 6+ and nasal midazolam for individuals aged 12+; buccal clonazepam is widely used off-label as rescue medication (Samanta 2021).

TABLE 7 | Consensus-achieving statements relating to the treatment and management of individuals with SGS.

Question type	Question/Statement	Percentage agreement	Responses included in analysis, *n*
General			
Likert-scale	Parents/caregivers should be engaged and educated as much as possible in order to facilitate a shared decision-making process	100	18
Likert-scale	All treatment and management decisions involving the care of an individual with SGS should be made through a well-informed shared decision-making model approach, involving the parents/caregivers	100	18
Specialist			
Multiple-choice	Neurologists should be standardly involved in the multidisciplinary treatment and management of individuals with SGS	88	16
Multiple-choice	Ophthalmologists and audiologists should be standardly involved in the multidisciplinary treatment and management of individuals with SGS[a]	94	16
Multiple-choice	Community/private duty nurses should be standardly involved in the multidisciplinary treatment and management of individuals with SGS	73	15
Multiple-choice	Complex care pediatricians should be standardly involved in the multidisciplinary treatment and management of individuals with SGS	80	15
Multiple-choice	Dietitians should be standardly involved in the multidisciplinary treatment and management of individuals with SGS	87	15
Multiple-choice	Geneticists should be standardly involved in the multidisciplinary treatment and management of individuals with SGS	80	15
Multiple-choice	Occupational therapists should be standardly involved in the multidisciplinary treatment and management of individuals with SGS	80	15
Multiple-choice	Palliative care specialists should be standardly involved in the multidisciplinary treatment and management of individuals with SGS	80	15
Multiple-choice	Physical therapists should be standardly involved in the multidisciplinary treatment and management of individuals with SGS	93	15
Multiple-choice	Speech and language therapists should be standardly involved in the multidisciplinary treatment and management of individuals with SGS	73	15
Multiple-choice	Nephrologists and urologists should be standardly involved in the multidisciplinary treatment and management of individuals with SGS	94	16
Multiple-choice	Pulmonologists should all be standardly involved in the multidisciplinary treatment and management of individuals with SGS	75	16
Likert-scale	Multisensory impairment (MSI) specialists (healthcare professionals who specialize in providing care for individuals who have impairments with both sight and hearing) should be standardly involved in the multidisciplinary treatment and management of individuals with SGS	100	17

(Continues)

TABLE 7 | (Continued)

Question type	Question/Statement	Percentage agreement	Responses included in analysis, *n*
Multiple-choice	Audiologists should be standardly involved (at least initially) in the multidisciplinary treatment and management of individuals with SGS (although this specialty should be consulted initially, it may be important for the clinician to monitor the individual with SGS continually)[b]	100	7
Multiple-choice	Cardiologists should be standardly involved (at least initially) in the multidisciplinary treatment and management of individuals with SGS (although this specialty should be consulted initially, it may be important for the clinician to monitor the individual with SGS continually)[b]	86	7
Multiple-choice	Ophthalmologists should be standardly involved (at least initially) in the multidisciplinary treatment and management of individuals with SGS (although this specialty should be consulted initially, it may be important for the clinician to monitor the individual with SGS continually)[b]	71	7
Multiple-choice	Orthopedic specialists should be standardly involved (at least initially) in the multidisciplinary treatment and management of individuals with SGS (although this specialty should be consulted initially, it may be important for the clinician to monitor the individual with SGS continually)[b]	71	7
Dermatology			
Likert-scale	A wound care referral should be made for the treatment and management of pressure sores and ulcers in individuals with SGS	100	15
Developmental pediatrics			
Likert-scale	Developmental delay should be managed by referral to a neurodisability specialist as well as an early intervention program in infancy (ages 0–3), followed by developmental pre-school	100	15
Likert-scale	Developmental delay should be managed by referral to physical and/or occupational therapy specialists	94	16
Likert-scale	Intensive speech and language therapy should be offered for individuals with SGS	93	15
Endocrinology			
Likert-scale	Standard pharmacological treatment strategies for hormonal regulation should be considered to manage seizures, mood changes and menstrual cycle irregularity	82	11
Gastroenterology			
Multiple-choice	A feeding tube should be utilized, if clinically indicated, for the management of aspiration in individuals with SGS	100	13
Multiple-choice	A feeding tube should be utilized, if clinically indicated, for the management of failure to thrive in individuals with SGS	100	13
Multiple-choice	Nasogastric tube feeding should be replaced with gastrostomy/jejunostomy tube feeding as soon as possible to facilitate feeding and medication administration	73	11
Multiple-choice	Standard pharmacological treatment should be used for the management of gastroesophageal reflux disease	100	11

(Continues)

TABLE 7 | (Continued)

Question type	Question/Statement	Percentage agreement	Responses included in analysis, *n*
Multiple-choice	Postural control should be used for the management of gastroesophageal reflux disease and gastroparesis	100	11
Multiple-choice	Continuous slow pump feeding should be used for the management of gastroesophageal reflux disease	91	11
Multiple-choice	Nissen fundoplication should be considered for the management of severe reflux and associated aspiration	91	11
Multiple-choice	Standard pharmacological treatment should be used for the management of gastroparesis	100	11
Multiple-choice	Continuous slow pump feeding should be used for the management of gastroparesis	91	11
Multiple-choice	Gastrostomy tube should be used for venting for the management of bloating and gastric distension	100	11
Multiple-choice	For continued concerns regarding aspiration and/or severe reflux in an individual with a gastrostomy tube, jejunostomy tube feeding should be considered	91	11
Multiple-choice	Day-to-day management of constipation should involve standard laxative pharmacological options, as indicated, and colonic irrigation and glycerin/warm water enemas	91	11
Likert-scale	A feeding tube should be utilized, if clinically indicated, for the management of gastrointestinal intolerance in individuals with SGS	100	13
Likert-scale	Jejunostomy tube feeding should be considered for continued concerns regarding aspiration and/or severe reflux in an individual with SGS with an existing g-tube	87	15
Likert-scale	Surgical procedures, such as colostomy, should be considered for severe dysmotility in individuals with SGS	90	10
Urology and nephrology			
Multiple-choice	Clean intermittent catheterization should be used to manage bladder atony	71	7
Multiple-choice	Prophylactic antibiotics should be used to manage urinary tract infection (UTI) recurrence	71	7
Multiple-choice	Clean intermittent catheterization should be used to manage UTI recurrence arising from neurologic bladder	86	7
Multiple-choice	Vesicostomy should be considered for managing urinary malformations/neurogenic bladder	71	7
Multiple-choice	Hydronephrosis should be actively treated/managed	86	7
Multiple-choice	Megacalycosis should be actively treated/managed	71	7
Multiple-choice	Nephrolithiasis should be actively treated/managed	100	7
Multiple-choice	Polycystic dysplastic kidney disease should be actively treated/managed[c]	100	7
Likert-scale	A Deflux procedure should be used to manage vesicoureteral reflux, if clinically indicated, in individuals with SGS	90	10
Likert-scale	Bladder catheterization should be used to manage hydronephrosis recurrence, if clinically indicated, in individuals with SGS	90	10

(Continues)

TABLE 7 | (Continued)

Question type	Question/Statement	Percentage agreement	Responses included in analysis, *n*
Likert-scale	Nephrostomy should be used to manage hydronephrosis recurrence, if clinically indicated, in individuals with SGS	91	11
Neurology			
Likert-scale	Rectal diazepam and/or midazolam (nasal or buccal) are standardly recommended medications for an epilepsy emergency plan for individuals with SGS	100	7
Oncology			
Likert-scale	A multidisciplinary team meeting with parents/caregivers involved should occur from the point of tumor identification to consider highly personalized treatment plans that factor in SGS comorbidities	100	13
Multisensory impairment			
Likert-scale	Vision therapy should be provided for individuals with SGS	100	11
Likert-scale	All individuals with SGS should be referred to a cerebral visual impairment specialist for educational support, should ophthalmological assessment fail to identify structural differences within the eye[d]	100	13
Likert-scale	All individuals with SGS should be referred to a cerebral visual impairment specialist for educational support, should visual impairment persist despite correction with interventions such as glasses[d]	100	13
Orthopedics			
Multiple-choice	Scoliosis may require the use of positioning devices (e.g., wheelchairs, orthotics, adaptive strollers)	100	8
Multiple-choice	Scoliosis may require the use of casting or splinting	88	8
Multiple-choice	Scoliosis may require surgical intervention	88	8
Multiple-choice	Hip dislocation may require the use of positioning devices (e.g., wheelchairs, orthotics, adaptive strollers)	75	8
Multiple-choice	Hip dislocation may require the use of casting or splinting	88	8
Multiple-choice	Hip dislocation may require surgical intervention	88	8
Multiple-choice	Contracture/tight tendons may be treated with botulinum toxin	100	8
Multiple-choice	Club feet/talipes may require the use of orthotics	100	8
Multiple-choice	Club feet/talipes may require surgical intervention	75	8
Otolaryngology			
Multiple-choice	Excessive salivation may be treated with anticholinergic medications	100	12
Multiple-choice	Excessive salivation may be treated with botulinum toxin injections	100	12
Multiple-choice	Dental caries may benefit from the provision of dental hygiene management advice	100	12
Likert-scale	Excessive salivation may be treated with excision of the salivary glands, if clinically indicated, in individuals with SGS	75	12

(Continues)

TABLE 7 | (Continued)

Question type	Question/Statement	Percentage agreement	Responses included in analysis, *n*
Palliative care			
Likert-scale	Early education of parents/caregivers (e.g., at diagnosis), with regards to what palliative care can entail and how a palliative care referral might be able to support them with day-to-day care and support, should be provided	100	17
Pulmonology			
Multiple-choice	Central sleep apnea may be managed by the use of supplemental oxygen	75	8
Multiple-choice	Aspiration of saliva may be managed by treatment with anticholinergic drugs	100	8
Multiple-choice	Frequent infections may be managed by chest physiotherapy	100	8
Multiple-choice	Accumulation of secretions in the airways may be managed by oral suction with a suction catheter or Yankauer suction tip	88	8
Multiple-choice	Accumulation of secretions in the airways may be managed by the use of an airway clearance vest	88	8
Multiple-choice	Accumulation of secretions in the airways may be managed by aggressive pulmonary hygiene, including the use of nebulizers	100	8
Multiple-choice	Recurrent pneumonia resulting from gastro-esophageal reflux may be managed by proton pump inhibitors	75	8
Multiple-choice	If clinically indicated, central sleep apnea may be managed by the use of positive airway pressure therapy in individuals with SGS	100	13
Likert-scale	The prevention, treatment and management of serious respiratory infections (e.g., pneumonia) should not differ for individuals with SGS compared to the general population (it is important to consider that, in many cases, individuals with SGS require a higher level of pulmonary care than the general population, both for day-to-day management and for the treatment of occurrent/recurrent pulmonary issues like pneumonia, for which individuals with SGS are at a higher risk)[b]	71	14
Likert-scale	All individuals with SGS should have an overnight polysomnography with full-lead EEG to rule out central and obstructive sleep apnea and hypoxic events which are related to physical characteristics of SGS	100	6

Note: Pink signifies statement achieved consensus in Round 1, blue signifies statement achieved consensus in Round 2, and yellow signifies statement achieved consensus in the virtual workshop.
Abbreviation: SGS, Schinzel-Giedion Syndrome.
[a]Options were restated in Round 2 due to technical error in question in Round 1.
[b]Information presented in brackets was noted by experts and informally agreed, but not formally voted upon by the entire expert panel.
[c]Experts noted that multicystic dysplastic kidney disease is the preferred term for the condition.
[d]'Cortical' was changed to 'cerebral' upon writing the manuscript questionnaire.

3.11 | Multisensory Impairment

Vision therapy should be provided for individuals with SGS. Furthermore, participants agreed that all individuals should be referred to a cerebral visual impairment specialist for educational support, should ophthalmological assessment fail to identify structural differences within the eye. In cases where structural differences within the eye are identified, a referral should be made to a cerebral visual impairment specialist for educational support if visual impairment persists despite corrective interventions (Table 7). Although not formally voted upon by the entire expert panel through the Delphi process, some experts noted that referral to a cerebral visual impairment specialist for educational support could also be considered in cases where corrective interventions are successful.

3.12 | Orthopedics

Consensus-achieving recommendations for the management of scoliosis, hip dislocation, contracture/tight tendons and club feet/talipes are reported in Table 7.

3.13 | Otolaryngology

Participants agreed that excessive salivation may be treated with anticholinergic medications, botulinum toxin injections and excision of salivary glands. Overall dental health (including the management/prevention of dental caries) may also benefit from the provision of dental hygiene management advice (Table 7).

3.14 | Pulmonology

Consensus-achieving recommendations for pulmonary issues including central sleep apnea, aspiration of saliva, frequent infections, accumulation of secretions in the airways, and recurrent pneumonia are reported in Table 7. Participants agreed that the prevention, treatment and management of serious respiratory infections (e.g., pneumonia) should align with that of the general population. Although not formally voted upon by the full expert panel, some experts noted that it is important to consider that in many cases, individuals with SGS require a higher level of pulmonary care than the general population, both for day-to-day management and for the treatment of occurrent/recurrent pulmonary issues like pneumonia, for which individuals with SGS are at a higher risk. Finally, all individuals with SGS should have an overnight polysomnography with full-lead EEG to rule out central and obstructive sleep apnea and hypoxic events which are related to physical characteristics of the condition. As consultation with a sleep specialist is likely necessary to obtain a sleep study, the individual taking primary care responsibility should make the initial referral, but the final decision on whether the test is needed should be made by the sleep specialist, who should be involved for the interpretation of the polysomnography.

4 | Discussion

SGS is an ultra-rare, life-limiting condition for which no SoC exists. Here, we present the first recommendations, achieved through a modified Delphi methodology, A brief plain regarding the diagnosis, monitoring, treatment and management of SGS. Across two rounds of questionnaires and a virtual workshop, a total of 94 consensus-seeking questions were asked to a panel of clinical experts, with 81 statements achieving consensus by the end of the process. It is hoped that this work will help to provide a basis for the standard care for this complex condition.

In Round 1, we sought to generate a new/modified set of definitive diagnostic criteria for SGS, including classic and atypical presentations. It quickly became apparent, however, that there is more work to be done to fully understand the phenotype, the condition's genetic basis, and genotype–phenotype correlations before experts would be comfortable providing such firm criteria. For example, although SGS is typically attributed to mutations within the *SETBP1* degron, a recently published case report described the first case of 'typical' (classic) SGS caused by a *SETBP1* non-degron pathogenic variant, thereby expanding the previously established genetic spectrum of SGS (Zheng et al. 2024). Thus, the Delphi process steered away from the pursuit of explicit diagnostic criteria-related recommendations and instead developed a set of core characteristics that, if present, should give clinicians the confidence to provide a working diagnosis of 'SGS' that is functionally adequate to encompass the spectrum of findings present in all *SETBP1*-gain-of-function pathogenic variants. As such, the recommendations laid out in this study should be considered a suitable starting point for the provision of high-quality care for individuals with confirmed and unconfirmed genetic diagnoses of SGS alike. Additionally, as more cases of SGS are identified that do not occur as a result of a *SETBP1*-gain-of-function pathogenic variant within the degron, the proposed recommendations outlined in this manuscript can be used to help guide clinicians.

Several key themes emerged from this Delphi process, including the involvement of healthcare professionals across a wide range of specialties in the care of individuals with SGS. These specialists should be engaged early on and throughout care, wherever possible. Furthermore, monitoring for the most common complications should occur regularly, and at an appropriate frequency, to closely monitor for the complication in question. Finally, all decisions involving the care of an individual with SGS should be made through a shared decision-making process; healthcare professionals providing care to an individual with SGS should aim to engage and educate parents/caregivers as much as possible.

Strengths of this study include the use of the Delphi technique, which has several methodological advantages when seeking expert consensus on a topic, including anonymity of responses to minimize bias. Additionally, this technique has been utilized on numerous occasions to develop SoC recommendations for other rare conditions, making it a well-established methodology in the field. The online nature of the questionnaires and virtual workshop allowed for the gathering of responses from geographically dispersed participants across a range of healthcare settings and specialties. Moreover, attrition over the questionnaire rounds was low.

However, this study is not without limitations. While a targeted literature review was undertaken to identify the existing body of relevant literature and develop the questionnaires, a full systematic review may have identified additional concepts and/or practices. Furthermore, the inherently long-term nature of a Delphi study means that the body of literature may have evolved since the targeted literature review was conducted. Regarding the expert panel, convenience sampling, based on connection with The SGS Foundation, was used to identify and invite participants; the included participants may therefore not be representative of the entire population of individuals with professional knowledge and experience within the management of complex care conditions. Finally, members of the expert panel were not comfortable voting on certain questions posed throughout the Delphi as they were phrased, limiting the extent to which conclusions could be drawn for these topics. Nevertheless, this study, supported by an international group of experts, presents an important contribution to the field.

5 | Conclusion

For the first time, a series of standard of care recommendations for SGS, developed in collaboration with a wide range of experts

from the USA and Europe using a modified Delphi technique, are provided. These recommendations have been developed with the intention of providing an accessible starting point and reference material for clinicians and families/caregivers of individuals with SGS alike, to inform care decisions, enhance quality and duration of life, and facilitate shared decision-making. With advances in our understanding of SGS and its effective management, it is hoped that these recommendations will be expanded upon by future work.

Author Contributions

Jessica Duis: substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Laura Agresta:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **William E. Bennett Jr:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Henry Chambers:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Antonia Clarke:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Charlie Fairhurst:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Julie Hoover-Fong:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Feilim Murphy:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Garey Noritz:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Scott Schwantes:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Michael Shreve:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Kabelo Thusang:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Darcy Weidemann:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Rebecca Beale:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Aditi Mehta:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Andrew Wilhelmsen:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published. **Nuala Summerfield:** substantial contributions to study conception and design, and analysis and interpretation of data, drafting the article or reviewing it critically for important intellectual content, final approval of the version of the article to be published.

Acknowledgments

The authors acknowledge Dr. Elizabeth Ames, Dr. Bregje van Bon, Dr. Carryn Cassidy, Dr. Kathryn Chatfield, Dr. Peter Yorgin, Dr. Susan Picton, Dr. Daniel Lesser, Dr. Inna Hughes, Professor Paul Gringras, and Dr. Jim Phillips for their involvement in the Delphi panel. The authors also acknowledge Naman Kochar and Emma Warnants, both of Costello Medical, London, UK, for their early involvement in the project. This Modified Delphi Study, and the subsequent development of this manuscript, was supported by Costello Medical free-of-charge, on a *pro bono* basis, for The Schinzel-Giedion Syndrome Foundation. Costello Medical supported the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation of the manuscript for publication; this support, including writing assistance for this article, was provided by Rebecca Beale, BSc, Andrew Wilhelmsen, PhD, and Aditi Mehta, MSc, Costello Medical, UK, in accordance with Good Publication Practice (GPP 2022) guidelines (https://www.ismpp.org/gpp-2022).

Ethics Statement

This work is not classified as research under the UK Policy Framework for Health and Social Care Research. This classification has been verified by the Medical Research Council Regulatory Support Centre tool developed in partnership with the Health Research Authority, which is based on the 'Defining Research' guidance produced by the Research Ethics Service. All participating experts provided written informed consent via email prior to participation and were explicitly instructed not to comment on individual patients. No patients were directly involved in the study, nor was patient-protected health information used. Therefore, ethics approval was not required.

Consent

The authors have nothing to report.

Conflicts of Interest

Jessica Duis: Employee of Neurocrine Biosciences. The opinions in this manuscript are her own and not in any way associated with that of Neurocrine Biosciences. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from Costello Medical upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.