Histopathology

Histopathology 2023 DOI: 10.1111/his.14902

Consensus based recommendations for the diagnosis of serous tubal intraepithelial carcinoma: an international Delphi study

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Date of submission 21 December 2022
Accepted for publication 25 February 2023
Published online *Article Accepted* xx-xx-xx

Bogaerts J M A, van Bommel M H D, Hermens R P M G, Steenbeek M P, de Hullu J A, van der Laak J A W M, STIC consortium & Simons M
(2023) *Histopathology*. https://doi.org/10.1111/his.14902

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Aim: Reliably diagnosing or safely excluding serous tubal intraepithelial carcinoma (STIC), a precursor lesion of tubo-ovarian high-grade serous carcinoma (HGSC), is crucial for individual patient care, for better understanding the oncogenesis of HGSC, and for safely investigating novel strategies to prevent tubo-ovarian carcinoma. To optimize STIC diagnosis and increase its reproducibility, we set up a three-round Delphi study.

Methods and results: In round 1, an international expert panel of 34 gynecologic pathologists, from 11 countries, was assembled to provide input regarding STIC diagnosis, which was used to develop a set of statements. In round 2, the panel rated their level of agreement with those statements on a 9-point Likert scale. In round 3, statements without previous consensus were rated again by the panel while anonymously disclosing the responses of the other panel members. Finally, each expert was asked to approve or disapprove the complete set of consensus statements. The panel indicated their level of agreement with 64 statements. A total of 27 statements (42%) reached consensus after three rounds. These statements reflect the entire diagnostic work-up for pathologists, regarding processing and macroscopy (three statements); microscopy (eight statements); immunohistochemistry (nine statements); interpretation and reporting (four statements); and miscellaneous (three statements). The final set of consensus statements was approved by 85%.

Conclusion: This study provides an overview of current clinical practice regarding STIC diagnosis amongst expert gynecopathologists. The experts' consensus statements form the basis for a set of recommendations, which may help towards more consistent STIC diagnosis.

Keywords: Delphi study, diagnostic consensus criteria, high-grade serous carcinoma (HGSC), serous tubal intraepithelial carcinoma (STIC)

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Introduction

Over the last decades, our understanding of the oncogenesis of extrauterine high-grade serous carcinoma (HGSC) has changed drastically. A number of precursor lesions to high-grade serous carcinoma can be found in the fallopian tube, ranging from the nearly normal-appearing p53 signatures to serous tubal intraepithelial carcinoma (STIC).[1–5] This range of precursor lesions and HGSC are bound together by shared *TP53* mutations. The genotoxic effects that lead to these *TP53* mutations are not yet fully understood, but the secretory cells in the fallopian tube seem most vulnerable.[6] Moreover, epigenetic effects may also play an important role towards the development of precursor lesions.[7] The incidence of isolated STIC varies from <0.1% in the general population up to around 3% in risk-reducing salpingo-oophorectomy specimens from women with an increased risk for developing HGSC, e.g. based on a *BRCA 1/2* pathogenic variant.[8,9] The combination of functional loss of *TP53* and *BRCA1/2* is therefore likely an important step in the development of HGSC.[10,11] For cases of HGSC, the reported incidence of STIC varies between 11 up to 61% of cases.[12]

Consistent and reproducible diagnosis of STIC lesions is crucial for three reasons. First, there are prognostic implications for individual patient care, given the significantly increased risk of peritoneal carcinomatosis that diagnosing an isolated STIC holds.[13] To what extent an isolated STIC should also have clinical implications, e.g. staging or chemotherapy, remains a subject of debate amongst treating clinicians. Second, consistent diagnosis of STIC will help further elucidate the aetiology of HGSC. Third, reliably diagnosing or excluding STIC is a prerequisite to safely investigate novel strategies to prevent tubo-ovarian cancer. Current international trials such as the TUBA-WISP II study (NCT04294927), the PROTECTOR study (ISRCTN25173360), and the SOROCK study (NCT04251052) are researching alternative risk-reducing strategies, in the form of risk-reducing salpingectomy with delayed oophorectomy. Reliably diagnosing or excluding STIC is important, as diagnosing STIC at salpingectomy would mandate an immediate oophorectomy.[14] By analogy, the same clinical implications would also apply to STIC lesions found in opportunistic salpingectomies. Diagnosing STIC may be a challenging task for pathologists, especially when it is present in isolation (without concurrent HGSC). Previous studies have shown moderate reproducibility amongst pathologists on haematoxylin and eosin (H&E)-stained slides.[15,16] Over the last years, multiple recommendations have been proposed to improve STIC diagnosis. For example, the Sectioning and Extensively Examining the FIMbriated End (SEE-FIM) protocol was developed, in which the entire fallopian tube is embedded with an explicit focus on the fimbriated end.[17] For microscopic evaluation, there are at least three different workflow recommendations, combining H&E examination with either standard or nonstandard additional immunohistochemical staining.[11,16,18] While these recommendations have made an important contribution to improving STIC diagnosis, they are generally based on the experiences of single institutions and focus on single aspects of the diagnosis, rather than the full diagnostic process. As such, they are inconsistently used by pathologists.

To optimize STIC diagnosis and improve its reproducibility, guidance on how to diagnose STIC is essential. However, evidence-based recommendations are currently unavailable. Therefore, we performed a Delphi study with an international panel of expert gynecologic pathologists in which we evaluated current practices and aimed to reach consensus on how the diagnostic work-up of STIC should be organised.

Materials and Methods

STUDY DESIGN

The Delphi method is a qualitative research tool, used for attaining group consensus via an iterative, multistage process with multiple rounds of anonymous surveys.[19–21] Rounds are held, aiming to achieve group consensus, according to predefined rules. The method can be specifically useful when there is ambiguity in diagnostic criteria, and when specific features need to be identified or agreed upon.[22]

We conducted a three-round Delphi study to systematically explore the opinions of expert gynecologic pathologists on the diagnosis of STIC. A flow diagram of the study is presented in Figure 1. Experts completed the rounds individually and anonymously to avoid potential social pressure. Experts had the possibility to adjust their opinion, as a result of being exposed to the anonymised replies of the other experts. All questionnaires were conducted using the electronic data management system CastorEDC. The Delphi rounds took place between September 2021 and April 2022. We used the following five study steps.

STEP 1: COMPOSITION OF THE EXPERT PANEL

Potential participants were identified via the MedLine database in which we searched for publications about

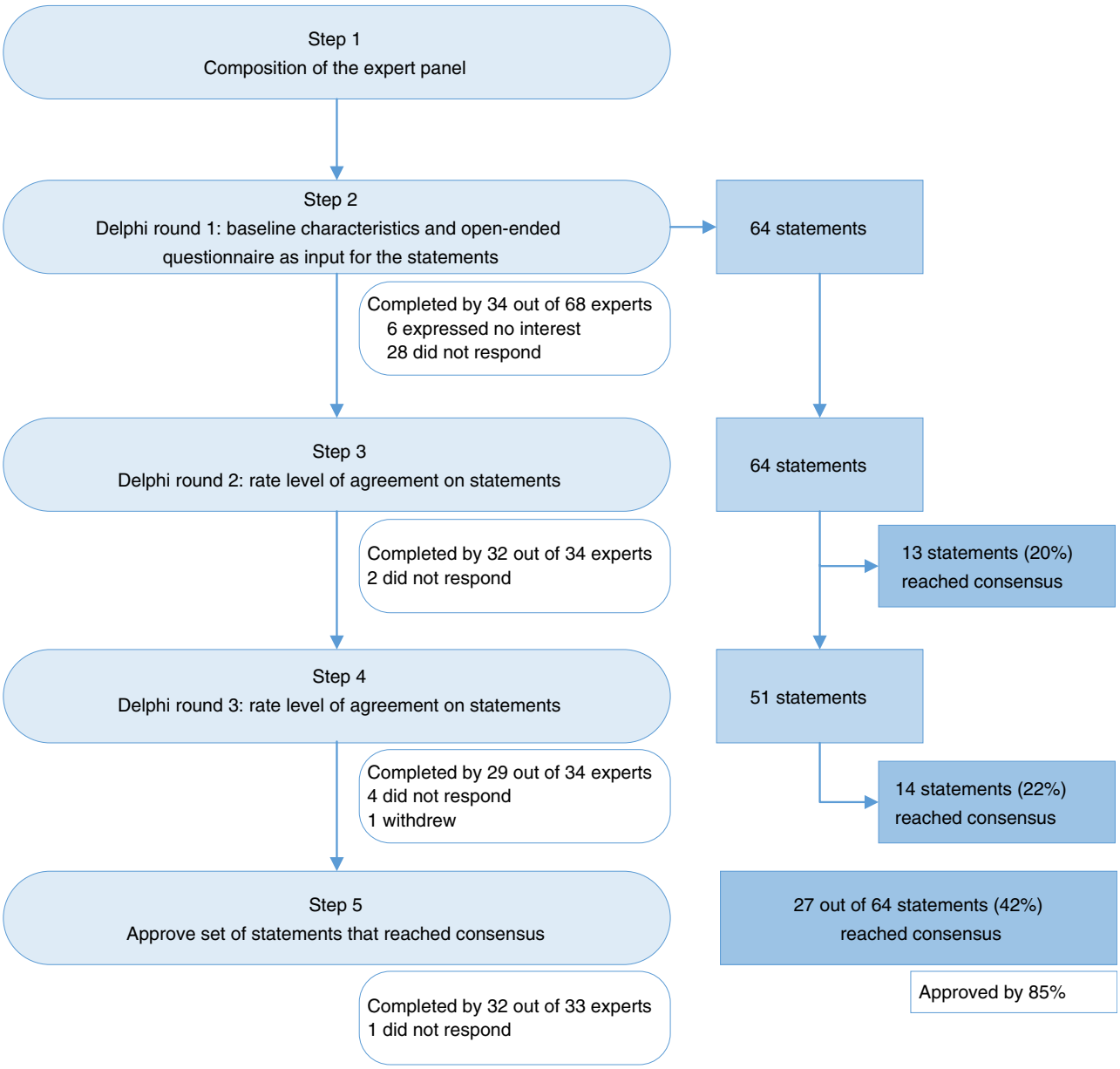

Figure 1. Study flowchart.

STIC in the past 5 years and they were contacted by e-mail. In addition, we invited pathologists within our international research network. All participants were invited to propose other eligible potential participants.

Experts were included if they (i) were (self-considered) subspecialised gynaecological pathologists, (ii) had demonstrable experience with STIC diagnosis (through published papers or clinical experience), and (iii) had sufficient English language proficiency.

STEP 2: DELPHI ROUND 1

The first Delphi round consisted of two questionnaires (supplementary Document S1). The first questionnaire was used to collect baseline characteristics of the participants, e.g. country of origin, years of working experience, etcetera. The second questionnaire aimed to gain insight into the experts' current diagnostic work-up for precursor lesions of HGSC in the fallopian tube. Experts were encouraged to add comments and provide suggestions for statements for successive rounds. All questions were open-ended to

stimulate experts in sharing their thoughts, without being restricted in any way.

All responses to the questionnaires were exported to IBM SPSS Statistics v. 25.0 (Armonk, NY, USA) in which they were encoded and grouped in domains independently, by two non-participating researchers (M.B. and J.B.). The responses were used to formulate statements on the diagnostic work-up for STIC for round 2. The statements were formulated to minimize ambiguous interpretations and were framed either positively or negatively based on the responses in round 1. The processing of the questionnaires was supervised by an independent nonvoting gynaecological pathologist (M.Si.).

STEP 3: DELPHI ROUND 2

Experts that completed the questions regarding baseline characteristics in round 1 were invited to participate in round 2. All experts were asked to rate their level of agreement on each statement on a 9-point Likert scale ranging from 1 'strongly disagree' to 9 'strongly agree'. Participants were given the option to add comments as well.

The results of round 2 were analysed using commonly used predefined consensus criteria.[23] Consensus on agreement was defined as ≥75% of participants scoring 'agree' (Likert score 7, 8, or 9). Consensus on disagreement was defined as ≥75% of participants scoring 'disagree' (Likert score 1, 2, or 3).[23] Statements that did not reach consensus were included in round 3.

STEP 4: DELPHI ROUND 3

All experts invited for round 2 were also invited for round 3. The questionnaire of round 3 included all statements that had not previously attained consensus. Personalised feedback forms were created for each participant, containing the interim results from round 2. These forms showed the group scores from the expert panel (anonymously), the median score, and their personal score in round 2 per statement (both consensus and nonconsensus statements). An example is shown in supplementary Document S2.

Participants were then asked to rate their agreement on the 9-point Likert scale again. Participants could reevaluate their opinion, taking into account the opinions of the other participants of the expert panel. The results of round 3 were analysed similarly to the results of round 2.

STEP 5: APPROVAL OF LIST OF CONSENSUS STATEMENTS

As a final step, a list of all statements that reached consensus was sent to each participant (supplementary Document S3). The participants were asked to either approve or disapprove this set to be used as recommendations to guide STIC diagnostics.

Results

STEP 1: COMPOSITION OF THE EXPERT PANEL

A total of 68 pathologists were invited to participate in this study. Fifty-five pathologists were identified via the Medline database search and 13 via our personal network, or by recommendation from other participants. A total of 34 pathologists responded and were invited to participate in the first round (response rate 50%).

STEP 2: DELPHI ROUND 1

The baseline characteristics of the 34 participating pathologists are presented in Table 1. Participants were from 11 countries worldwide with a median (range) work experience in gynecopathology of 15 (3–32) years. The questionnaire of the first Delphi round was completed by 32 participants (94%). From these answers, 64 statements were developed (Figure 1). The statements were subdivided into five domains representing the complete diagnostic work-up for pathologists; processing and macroscopy (six statements); microscopy (23 statements); immunohistochemistry (16 statements); interpretation and reporting (11 statements); and miscellaneous (eight statements).

STEP 3: DELPHI ROUND 2

The questionnaire of Delphi round 2 was completed by 32 participants (94%). A total of 13 out of 64 statements reached consensus (20%) (Figure 1). Of these 13 statements, six reached consensus based on agreement and seven based on disagreement. The other 51 statements did not reach consensus and were assessed again in round 3.

STEP 4: DELPHI ROUND 3

A total of 29 participants (85%) completed round 3. The two nonresponders in round 2 completed round 3. One participant withdrew from the study. An additional 14 statements reached consensus in round 3,

Table 1. Background characteristics of the expert panel

	Gynecologic pathologists (*N* = 34)	
	N/ median	%/ range
Type of center		
Academic medical center	34	100%
Number of gynecologic pathologist colleagues	3	1–11
Country		
Australia	1	3%
Austria	1	3%
Belgium	1	3%
Canada	2	6%
France	1	3%
Germany	1	3%
Ireland	1	3%
Sweden	1	3%
The Netherlands	6	18%
UK	4	12%
USA	15	44%
Experience in the field, years		
Pathology	19.5	3–36
Gynecologic pathology	15.0	3–32
Experience in the field, diagnosis per year		
Ovarian cancer	100	25–600
STIC	15	1–90
Currently active in		
Clinical practice	33	97%
Research	27	79%
Training	34	100%
Reviewing potential STICs from other centers	30	88%
Self-considered gynecologic pathologist	33	97%
Feeling with diagnosing STIC		
Very uncomfortable	6	18%
Uncomfortable	0	0%
Neutral	1	3%
Comfortable	15	44%
Very comfortable	12	35%

N, Number of participants; STIC, Serous tubal intraepithelial carcinoma.

reaching a total of 27 consensus statements. Out of these, 13 were based on agreement (48%) and 14 based on disagreement (52%). (Figure 1 and supplementary Document S3.)

CONSENSUS STATEMENTS

All statements and the opinion of the expert panel per statement can be found in supplementary Document S4. Statements that reached consensus are presented in Figure 2. Focusing on the statements that reached consensus based on agreement, we see that, with regard to processing and macroscopy, there was consensus that each fallopian tube (regardless of indication for salpingectomy) should have the fimbriated end fully embedded for microscopic examination. Regarding microscopy, the panel agreed that STIC shows an abrupt transition from background epithelium and that cytologic features in STIC are identical to the cells of HGSC. Distinctive cytologic changes are nuclear pleomorphism, nuclear enlargement, high nuclear-to-cytoplasmic ratio, and nuclear hyperchromasia. With regard to immunohistochemistry, there was consensus that p53 and Ki67 staining only have to be performed in cases with abnormal morphology and that an aberrant p53 staining is mandatory for diagnosing STIC. In the group of miscellaneous statements, there was consensus that an incidental STIC diagnosis indicates the need for genetic testing (if not previously performed). The complete set of clinical recommendations extracted from the consensus statements are presented in Figure 3.

STEP 5: APPROVAL OF LIST OF CONSENSUS STATEMENTS

The list of 27 consensus statements was approved by 85% of the panel (28/33). One pathologist did not respond and four voted against. Three of the four

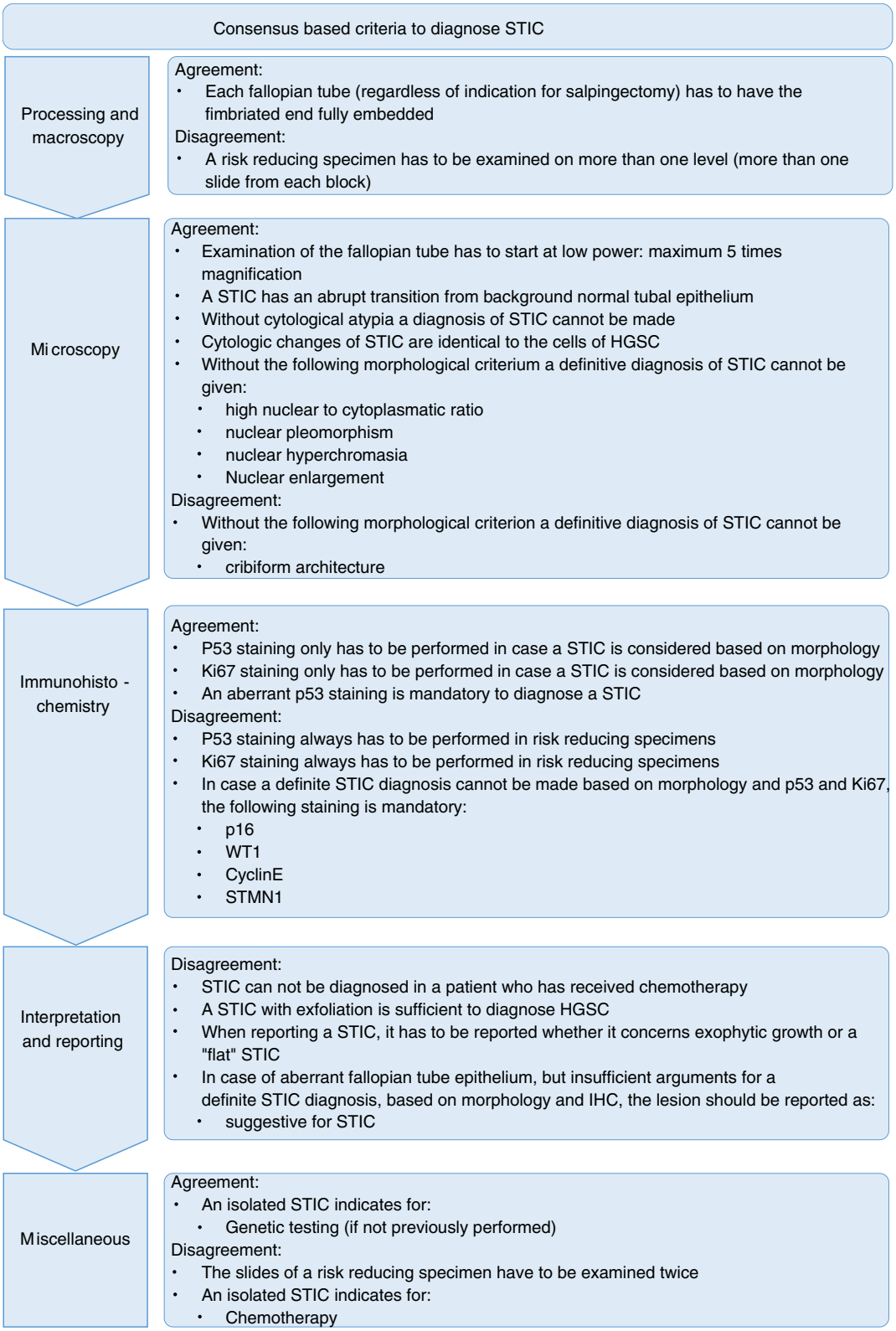

Figure 2. Statements that reached consensus visualized per domain. Statements reached consensus, either based on agreement or based on disagreement.

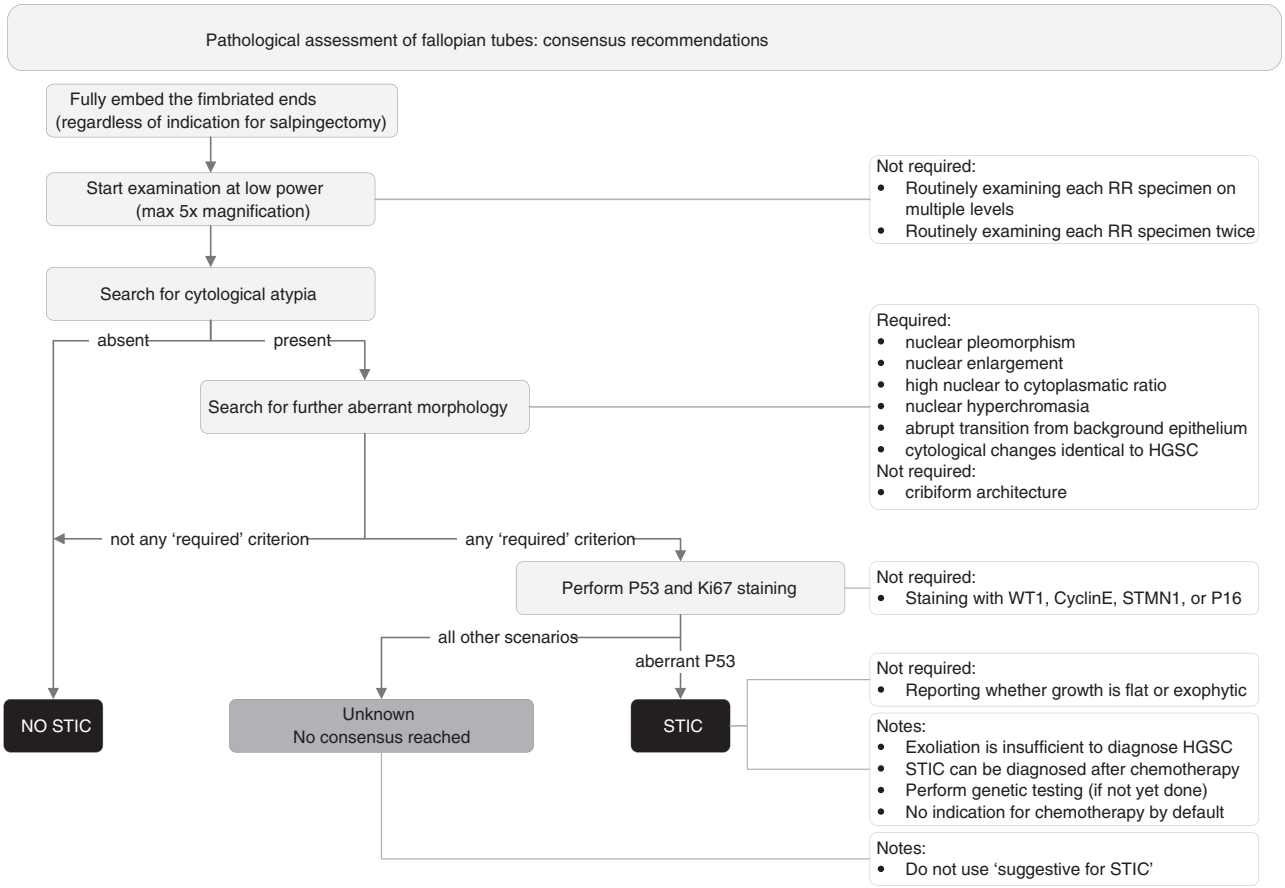

Figure 3. Clinical flowchart.

participants that disapproved the set mentioned that this was solely based on disagreement with a single statement ('An aberrant p53 staining is mandatory to diagnose an STIC').

Discussion

In this Delphi study, we propose recommendations to guide STIC diagnosis, based on consensus from an international expert panel of 34 gynecologic pathologists. These recommendations are based on 27 consensus statements, which can be subdivided into five domains that reflect the full diagnostic work-up performed by a pathologist: processing and macroscopy, microscopy, immunohistochemistry, interpretation and reporting, and miscellaneous. The final set of statements that reached consensus was supported by 85% of the experts. This set forms the basis for a flowchart that provides practical recommendations for pathologists, on how to organize their diagnostic approach to fallopian tube specimens (Figure 3). The pathologist should start the examination of a slide at low magnification and look for areas that show cytological atypia, i.e. areas that stand out. If cytological atypia is present, the pathologist should examine that area at a higher magnification and look for the distinctive morphological characteristics on which consensus was reached that an STIC should have. If these are present the pathologist should use immunohistochemistry to further support the diagnosis.

Regarding processing and macroscopy, there was consensus that the fimbriated end of the fallopian tube should be fully embedded in all cases, regardless of the indication for surgery. However, statements regarding use of the SEE-FIM protocol did not reach consensus. This likely reflects the variation in practice amongst gynecologic pathologists, with some using this in all salpingectomies, some only in cases of gynecologic malignancies, and some only in cases of extrauterine HGSC.[24] The SEE-FIM protocol was developed to maximize the amount of fallopian tube epithelium to be examined histologically, and dictates the entire tube to be embedded for

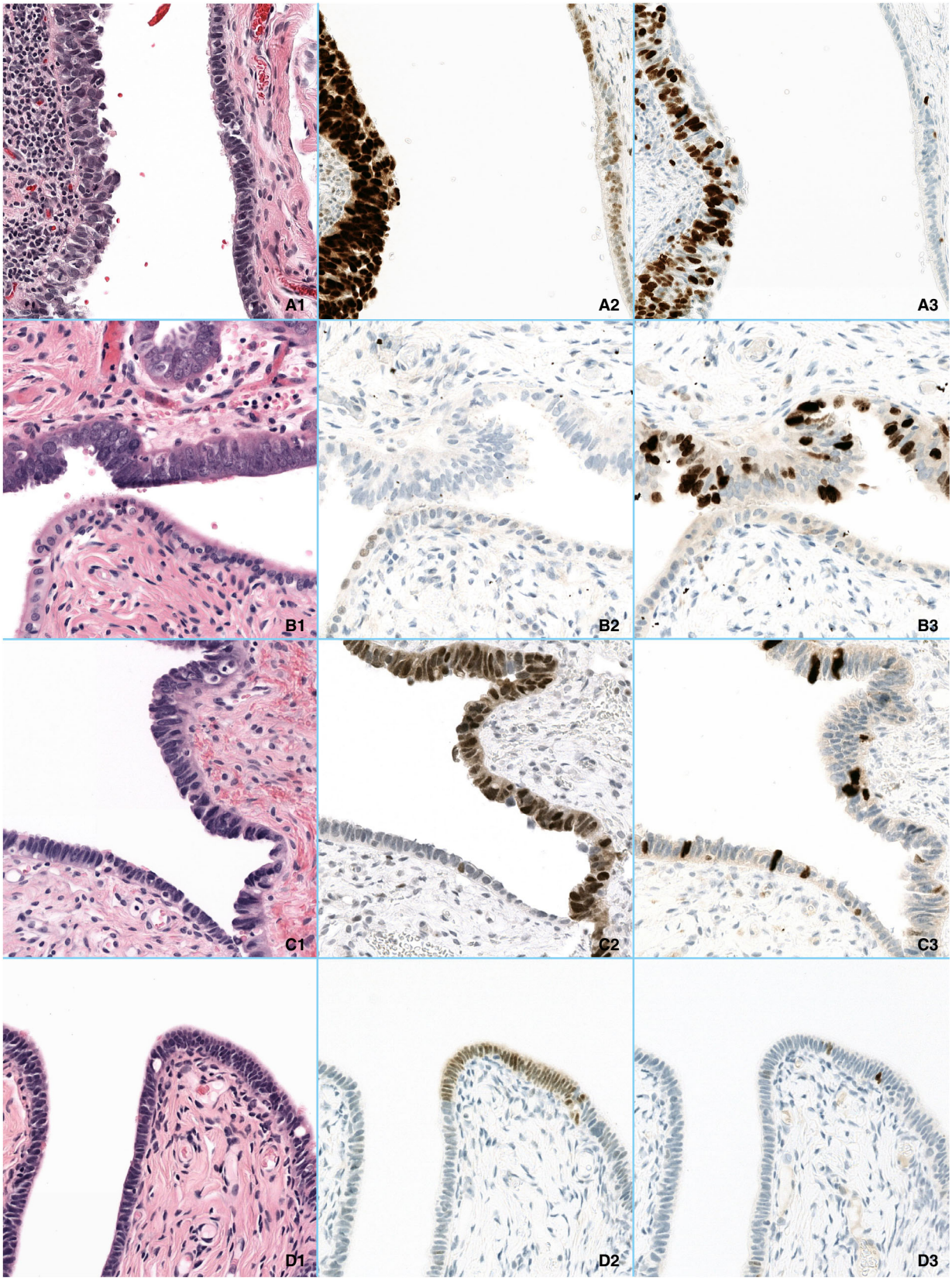

Figure 4. **A1**: H&E stain with an STIC lesion (left-hand side). There is nuclear pleomorphism, nuclear enlargement, a high nuclear-to-cytoplasmic ratio, and hyperchromasia. The cytological atypia stands out compared to the normal epithelium (right-hand side). Corresponding p53 immunostain shows an overexpression pattern (**A2**). Ki67 shows an increased proliferation index (PI) (**A3**). Case B shows another STIC lesion, with characteristic cytomorphological atypia on H&E (**B1**), a complete lack of p53 staining (**B2**), and an increased PI in the Ki67 (**B3**). Case C shows an STIL lesion, with less obvious cytomorphologic atypia (**C1**), an overexpression pattern in P53 (**C2**) but no increased PI in Ki67 (**C3**). Case D shows a p53 signature. There is no noteworthy atypia on H&E (**D1**), an overexpression in P53 (**D2**), and no increased PI in the Ki67 (**D3**). These images are for illustrative purposes. The diagnoses are not a result of this Delphi study.

microscopic examination.[17] The use of the SEE-FIM protocol results in an increased detection of STIC, which is particularly relevant for women at increased inherited risk of tubo-ovarian cancer.[25] However, this protocol leads to increased work for laboratory technicians and pathologists, compared to representative sampling. Given the small chance of finding an STIC lesion in the general population (0.1%), members of the expert panel argued that the cost–benefit was too low to apply the SEE-FIM protocol by default.[8,26] That the use of the SEE-FIM protocol in risk-reducing specimens and cases of gynecologic malignancy did not reach consensus may be explained by the reasoning of some experts that an STIC has no clinical consequence when diagnosed concomitant to HGSC and no other gynecologic malignancies are associated with STIC. Unfortunately, we did not include a statement that specifically proposed the use of this protocol in risk-reducing specimens, although such a statement would likely have reached consensus. Moreover, current national and international guidelines and study protocols state that the SEE-FIM protocol is recommended in risk-reducing specimens.[27–29]

Regarding immunohistochemistry, there was consensus that an aberrant p53 staining is mandatory for diagnosing STIC. This statement was the reason for three participants disapproving the set of consensus statements. P53 immunostaining can be used as a surrogate to determine the presence of *TP53* mutations. In the normal Fallopian tube epithelium, one would expect a wildtype staining pattern. Aberrant staining patterns consist of overexpression, which is correlated with missense mutation, or a complete lack of staining, which is correlated with a null mutation. A third, rare aberrant staining pattern is recognised as cytoplasmic staining.[30–32] The counterargument from the participants opposing this statement was that only 96.7% of tubo-ovarian HGSCs exhibit aberrant/mutation-type p53 staining in spite of the presence of an underlying pathogenic *TP53* mutation, and that one can assume that the same would be true for STIC.[30,33,34] In addition, considering the often small size of an STIC lesion, the lesion may be "cut out" when additional sections are stained immunohistochemically. The role of Ki67 immunohistochemical staining is also an issue of debate. Consensus was reached that Ki67 should be performed in cases with a morphological abnormality, but no consensus was reached on its interpretation, i.e. there was no consensus if Ki-67 should show an increased proliferative index in order to diagnose STIC. Ki67 is a widely used cell proliferation marker. Based on previous reproducibility studies, a proliferation index higher than 10% is often considered abnormal within the fallopian tube and this has been used as a criterion to diagnose STIC.[16,35,36] However, Ki67 staining is known to be prone to interlaboratory variability, which makes it difficult to standardize cutoff values.[37] This may partly be due to the use of various stainer platforms and commercially available clones of Ki67, such as Mib1, SP6, MM1, and 30.9, which were shown to result in significantly different proliferation indices in cases of breast cancer.[38] A more pragmatic approach, whereby the pathologist looks for an increase, relative to the background epithelium, was therefore suggested by a number of the participants and presented to the panel, but did not reach consensus.

With regard to interpretation and reporting, we can see continued discussion on how to diagnose the spectrum of lesions that fall short of a diagnosis of STIC and what nomenclature is best suited. The morphologically least affected of these lesions are p53 signatures, which are characterised by an aberrant p53 staining pattern in at least 12 adjacent cells, but no clear cytomorphological atypia in the H&E staining. Such lesions can be found in up to 50% of all fallopian tube specimens and are thought to be an early event in the pathway to serous carcinoma.[11] STIL, TILT, and serous tubal epithelial proliferation of uncertain significance are all terms used for lesions that show more obvious cytological atypia. These lesions may resemble STIC, but fall short of this diagnosis because the cytological atypia is deemed insufficient, or in the case of STIL and TILT, because immunohistochemical stains for p53 and Ki-67 do not fully support that diagnosis.[11,16,39] The term early serous proliferations is also sometimes encountered in the literature, and is used as an umbrella

term for all lesions that lack the full cytomorphologic features of STIC, but contain *TP53* mutations.[40] An illustrative set of examples of STIC, STIL, and p53 signature lesions is shown in Figure 4. Finally, there is another group of proliferative lesions in the fallopian tube epithelium, which are not linked to *TP53* mutations, but may demonstrate overlapping cytologic changes with the other lesions. These lesions are referred to as secretory or stem cell outgrowths (SCOUTs). SCOUTS are found at an increased rate in women with serous carcinoma, although there is no evidence that they are directly related.[11,41] The clinical value of all these different lesions and to what extent they should lead to further clinical action, especially when diagnosed in isolation, remains unclarified. This is likely due to the lack of data concerning their biology and potential to progress into malignancy. It may be that this spectrum of precursor lesions follow each other sequentially, but given that there are also HGSC cases, in which no STIC is found, alternative theories have been postulated in which other early serous proliferations, such as p53 signatures or STIL, lead to HGSC via a "precursor escape" model.[40,42] Further research regarding the spectrum from normal tubal epithelium to HGSC would contribute to a better understanding of the oncogenesis of HGSC. Consensus on the most appropriate terminology for lesions falling short of STIC was not reached. Lack of consistent terminology has the potential to complicate communication between medical specialists, both in patient care and research, and thus requires further attention.

In conclusion, diagnosing STIC can be challenging and unreproducible, as the lesion is often small, the condition is rare in isolation (without HGSC), and there is little uniformity in the diagnostic criteria used. In this study we give an overview of current clinical practice amongst expert gynecologic pathologists and present consensus-based recommendations to guide the process of diagnosing STIC. Next to these consensus-based recommendations, this study also highlights areas of ongoing discussion where opinions amongst expert pathologists still diverge, and which stand to benefit from further research. Our study is unique, as we were able to put together a panel with 34 experts from 11 countries across the world. The size of the group as well the heterogeneity are considerable strengths of this study. Therefore, the consensus opinion of this group is very likely applicable to a wide range of practice settings. Limitations of our study include the non-responses of some participants and that, despite careful framing, some statements might have been prone to ambiguous interpretations. Inherent to the Delphi study design, the experts' reasoning for disagreement with a statement is not always clear. Therefore, extending this study with a consensus meeting or a follow-up study to analyse pathologists' consistency in diagnosing STIC using the presented guidelines may be valuable. Continued international collaboration and the creation of a consortium of patients with isolated STIC may further contribute to a reliable and reproducible STIC diagnosis, which in turn will help to further unravel HGSC aetiology, improve individual patient management, and safely investigate new risk-reducing treatment options.

Author contributions

J.B., M.B., R.H., M.St., J.H., J.L., and M.Si. performed study concept, design, and development of methodology; J.B. and M.B. performed writing; R.H., M.St., J.H., J.L., M.Si., and the members of the STIC consortium performed review and revision of the article; J.B., M.B., R.H., M.St., J.H., J.L., M.Si., and the members of the STIC consortium provided acquisition, analysis and interpretation of data, and statistical analysis; All authors read and approved the final article.

Conflict of interest

The authors declare no competing financial interests.

Funding information

This project received financial support from the Dutch Cancer Society (KWF kankerbestrijding).

Data availability statement

The data used during the current study is available from the corresponding author on reasonable request.

References

1. Piek JMJ, Van Diest PJ, Zweemer RP *et al*. Dysplastic changes in prophylactically removed fallopian tubes of women predisposed to developing ovarian cancer. *J. Pathol.* 2001; **195**; 451–456.
2. Shih IM, Wang Y, Wang TL. The origin of ovarian cancer species and precancerous landscape. *Am. J. Pathol.* 2021; **191**; 26–39.

3. Glenn Mccluggage W, Judge MJ, Clarke BA *et al*. Data set for reporting of ovary, fallopian tube and primary peritoneal carcinoma: recommendations from the international collaboration on cancer reporting (ICCR). *Mod. Pathol.* 2015; **28**; 1101–1122.
4. Singh N, Gilks CB, Hirschowitz L *et al*. Primary site assignment in tubo-ovarian high-grade serous carcinoma: Consensus statement on unifying practice worldwide. *Gynecol. Oncol.* 2016; **141**; 195–198.
5. Kuhn E, Meeker A, Wang TL, Sehdev AS, Kurman RJ, Shih IM. Shortened telomeres in serous tubal intraepithelial carcinoma: An early event in ovarian high-grade serous carcinogenesis. *Am. J. Surg. Pathol.* 2010; **34**; 829–836.
6. Perets R, Wyant GA, Muto KW *et al*. Transformation of the fallopian tube secretory epithelium leads to high-grade serous ovarian cancer in Brca;Tp53;Pten models. *Cancer Cell* 2013; **24**; 751–765.
7. Bartlett TE, Chindera K, McDermott J *et al*. Epigenetic reprogramming of fallopian tube fimbriae in BRCA mutation carriers defines early ovarian cancer evolution. *Nat. Commun.* 2016; **7**; 7.
8. Samimi G, Trabert B, Geczik AM, Duggan MA, Sherman ME. Population frequency of serous tubal intraepithelial carcinoma (STIC) in clinical practice using SEE-Fim protocol. *JNCI Cancer Spectr.* 2018; **2**; pky061. https://doi.org/10.1093/jncics/pky061.
9. Bogaerts JMA, Steenbeek MP, van Bommel MHD *et al*. Recommendations for diagnosing STIC: a systematic review and meta-analysis. *Virchows Arch.* 2021; **480**; 725–737.
10. Norquist BM, Garcia RL, Allison KH *et al*. The molecular pathogenesis of hereditary ovarian carcinoma. *Cancer* 2010; **116**; 5261–5271.
11. Meserve EE, Brouwer J, Crum CP. Serous tubal intraepithelial neoplasia: The concept and its application. *Mod. Pathol.* 2017; **30**; 710–721.
12. Chen F, Gaitskell K, Garcia MJ, Albukhari A, Tsaltas J, Ahmed AA. Serous tubal intraepithelial carcinomas associated with high-grade serous ovarian carcinomas: a systematic review. *BJOG An Int. J. Obstet. Gynaecol.* 2017; **124**; 872–878.
13. Steenbeek MP, van Bommel MHD, Bulten J *et al*. Risk of peritoneal carcinomatosis after risk-reducing Salpingo-oophorectomy: a systematic review and individual patient data meta-analysis. *J. Clin. Oncol.* 2022; **40**; JCO2102016–JCO2101891.
14. Huh WK, Pugh SL, Walker JL *et al*. NRG-CC008: a nonrandomized prospective clinical trial comparing the noninferiority of salpingectomy to salpingo-oophorectomy to reduce the risk of ovarian cancer among BRCA1 carriers [SOROCk]. 2022; **40**; TPS10615.
15. Carlson JW, Jarboe EA, Kindelberger D, Nucci MR, Hirsch MS, Crum CP. Serous tubal intraepithelial carcinoma: Diagnostic reproducibility and its implications. *Int. J. Gynecol. Pathol.* 2010; **29**; 310–314.
16. Visvanathan K, Vang R, Shaw P *et al*. Diagnosis of serous tubal intraepithelial carcinoma based on morphologic and immunohistochemical features. *Am. J. Surg. Pathol.* 2011; **35**; 1766–1775.
17. Medeiros F, Muto MG, Lee Y *et al*. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. *Am. J. Surg. Pathol.* 2006; **30**; 230–236.
18. Perrone ME, Reder NP, Agoff SN *et al*. An alternate diagnostic algorithm for the diagnosis of intraepithelial fallopian tube lesions. *Int. J. Gynecol. Pathol.* 2020; **39**; 261–269.
19. Dalkey N, Brown B, Cochran S. *The Delphi method III; use of self ratings to improve group estimates. Group estimates*. Rand: Santa Monica, CA, 1969.
20. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR. The RAND/UCLA appropriateness method user's manual; 2001.
21. Boulkedid R, Abdoul H, Loustau M, Sibony O, Alberti C. Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review. *PLoS One* 2011; **6**; 20476.
22. Taze D, Hartley C, Morgan AW, Chakrabarty A, Mackie SL, Griffin KJ. Developing consensus in histopathology: The role of the Delphi method. *Histopathology* 2022; **81**; 159–167.
23. Diamond IR, Grant RC, Feldman BM *et al*. Defining consensus: A systematic review recommends methodologic criteria for reporting of Delphi studies. *J. Clin. Epidemiol.* 2014; **67**; 401–409.
24. Samimi G, Trabert B, Duggan MA *et al*. Processing of fallopian tube, ovary, and endometrial surgical pathology specimens: a survey of U.S. laboratory practices. *Gynecol. Oncol.* 2018; **148**; 515–520.
25. Koc N, Ayas S, Arinkan SA. Comparison of the classical method and SEE-FIM protocol in detecting microscopic lesions in fallopian tubes with gynecological lesions. *J. Pathol. Transl. Med.* 2018; **52**; 21–27.
26. Meserve EEK, Mirkovic J, Conner JR *et al*. Frequency of "incidental" serous tubal intraepithelial carcinoma (STIC) in women without a history of or genetic risk factor for high-grade serous carcinoma: a six-year study. *Gynecol. Oncol.* 2017; **146**; 69–73.
27. Protocol for the Examination of Specimens From Patients With Primary Tumors of the Ovary, Fallopian Tube, or Peritoneum; 2022. Available at: www.cap.org/cancerprotocols. Accessed July 12, 2022.
28. Erfelijk en familiair ovariumcarcinoom - Preventieve chirurgie - Richtlijn - Richtlijnendatabase. Available at: https://richtlijnendatabase.nl/richtlijn/erfelijk_en_familiair_ovariumcarcinoom_iknl/preventieve_chirurgie.html. Accessed July 12, 2022.
29. Ovary, Fallopian Tube and Primary Peritoneal Carcinomas - ICCR. Available at: https://www.iccr-cancer.org/datasets/published-datasets/female-reproductive/ovary-ft-pp/. Accessed August 11, 2022.
30. Kuhn E, Kurman RJ, Vang R *et al*. TP53 mutations in serous tubal intraepithelial carcinoma and concurrent pelvic high-grade serous carcinoma-evidence supporting the clonal relationship of the two lesions. *J. Pathol.* 2012; **226**; 421–426.
31. Rabban JT, Garg K, Ladwig NR, Zaloudek CJ, Devine WP. Cytoplasmic pattern p53 Immunoexpression in pelvic and endometrial carcinomas with TP53 mutation involving nuclear localization domains: an uncommon but potential diagnostic pitfall with clinical implications. *Am. J. Surg. Pathol.* 2021; **45**; 45–1451.
32. Köbel M, Mccluggage G, Gilks CB, et al. *Guidance document: p53 IHC reporting in tubo-ovarian carcinoma version 1 interpretation of p53 immunohistochemistry In Tubo-ovarian carcinoma: Guidelines for reporting*. 2016. Available at: https://www.bgcs.org.uk/wp-content/uploads/2019/05/BAGP-UKNEQAS-project-p53-interpretation-guide-2016.pdf. Accessed March 13, 2023.
33. Ahmed AA, Etemadmoghadam D, Temple J *et al*. Driver mutations in TP53 are ubiquitous in high grade serous carcinoma of the ovary. *J. Pathol.* 2010; **221**; 49–56.
34. Köbel M, Piskorz AM, Lee S *et al*. Optimized p53 immunohistochemistry is an accurate predictor of TP53 mutation in ovarian carcinoma. *J. Pathol. Clin. Res.* 2016; **2**; 247–258.
35. Vang R, Visvanathan K, Gross A *et al*. Validation of an algorithm for the diagnosis of serous tubal intraepithelial carcinoma. *Int. J. Gynecol. Pathol.* 2012; **31**; 243–253.

36. Herrington CS, Board WC of TE. Female genital Tumours, WHO classification of Tumours. 5th ed. 2020. Available at: https://www.research.ed.ac.uk/en/publications/who-classification-of-tumours-female-genital-tumours. Accessed January 24, 2023.
37. Polley MYC, Leung SCY, McShane LM *et al.* An international ki67 reproducibility study. *J. Natl. Cancer Inst.* 2013; **105**; 1897–1906.
38. Røge R, Nielsen S, Riber-Hansen R, Vyberg M. Impact of primary antibody clone, format, and Stainer platform on Ki67 proliferation indices in breast carcinomas. *Appl. Immunohistochem. Mol. Morphol.* 2019; **27**; 732–739.
39. Leonhardt K, Einenkel J, Sohr S, Engeland K, Horn LC. P53 signature and serous tubal in-situ carcinoma in cases of primary tubal and peritoneal carcinomas and serous borderline tumors of the ovary. *Int. J. Gynecol. Pathol.* 2011; **30**; 417–424.
40. Soong TR, Howitt BE, Horowitz N, Nucci MR, Crum CP. The fallopian tube, "precursor escape" and narrowing the knowledge gap to the origins of high-grade serous carcinoma. *Gynecol. Oncol.* 2019; **152**; 426–433.
41. Chen EY, Mehra K, Mehrad M *et al.* Secretory cell outgrowth, PAX2 and serous carcinogenesis in the fallopian tube. *J. Pathol.* 2010; **222**; 110–116.
42. Jarboe EA, Folkins AK, Drapkin R, Ince TA, Agoston ES, Crum CP. Tubal and ovarian pathways to pelvic epithelial cancer: A pathological perspective. *Histopathology* 2008; **53**; 127–138.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

File S1. The questionnaires of Delphi round 1.

File S2. Personalized feedback form with interim results from round 2.

File S3. Consensus statements.

File S4. Final results of all statements.

Appendix

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