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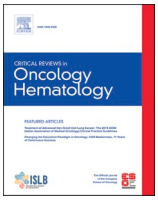

International consensus on the initial diagnostic workup of cancer of unknown primary

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ABSTRACT

Background: Although the incidence of Cancer of Unknown Primary (CUP) is estimated to be 1–2 % of all cancers worldwide, no international standards for diagnostic workup are yet established. Such an international guideline would facilitate international comparison, provide adequate incidence and survival rates, and ultimately improve care of patients with CUP.

Methods: Participants for a four round modified Delphi study were selected via a CUP literature search in PubMed and an international network of cancer researchers. A total of 90 CUP experts were invited, and 34 experts from 15 countries over four continents completed all Delphi survey rounds.

Findings: The Delphi procedure resulted in a multi-layer CUP classification for the diagnostic workup. Initial diagnostic workup should at least consist of history and physical examination, full blood count, analysis of serum markers, a biopsy of the most accessible lesion, a CT scan of chest/abdomen/pelvis, and immunohistochemical testing. Additionally, the expert panel agreed on the need of an ideal diagnostic lead time for CUP patients. There was no full consensus on the place in diagnostic workup of symptom-guided MRI or ultrasound, a PET/CT scan, targeted gene panels, immunohistochemical markers, and whole genome sequencing.

Interpretation: Consensus was reached on the contents of the first diagnostic layer of a multi-layer CUP classification. This is a first step towards full consensus on CUP diagnostics, that should also include supplementary and advanced diagnostics.

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1. Introduction

Cancer imposes the largest worldwide burden of all diseases, accounting for an estimated 19.3 million new cancer cases and almost ten million deaths in 2020 (Sung et al., 2021). In most of the cases, the site of origin of the cancer is clear at presentation or identified soon after. However, in approximately 1–2 % of cancer cases, the site of origin cannot be detected with current diagnostic strategies, and the cancer remains of unknown primary origin (CUP) (Rassy and Pavlidis, 2019; Fizazi et al., 2015a; Kolling et al., 2019; Pavlidis and Pentheroudakis, 2012; Urban et al., 2013). The diagnosis of CUP is preferentially made when other primary cancers have been ruled out and is based on a combination of imaging techniques, as well as clinical and histopathological examination (Massard et al., 2011; van de Wouw et al., 2002). Since cancer treatment in general is based on the primary tumour, this represents a huge dilemma for both CUP patients and healthcare professionals (Kolling et al., 2019). The median survival of CUP patients ranges from three months up to five years. Most common metastatic sites include the liver, lymph nodes, lungs, and bones (Hess et al., 1999; Schroten-Loef et al., 2018; Ponce Lorenzo et al., 2007; Randen et al., 2013; Pavlidis and Fizazi, 2009; Moran et al., 2017).

Currently, there is no international consensus on the diagnostic workup for patients with CUP, which makes a reliable international comparison between CUP patient populations impossible. In addition, the lack of consensus has an impact on the quality of care provided to patients with CUP. Guidelines on CUP such as the Dutch Oncoline, as well as the English written guidelines on CUP from the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), the National Institute of Health and Care Excellence (NICE), and the Spanish Society of Medical Oncology (SEOM) show overlap, but there are numerous differences in the recommended diagnostic workup (Fizazi et al., 2015a; Specialists, 2012; Ettinger et al., 2021; Excellence, 2010; Losa et al., 2018a). Although the NICE guideline categorizes CUP into malignancy of unknown origin (MUO), provisional CUP (pCUP), and confirmed CUP (cCUP), the diagnostic techniques used per category are not specified (Excellence, 2010).

To the best of our knowledge, no previous attempts have been made to work towards a international consensus on CUP diagnostics. In 2015, a comparison between different CUP guidelines was performed, that showed differences in imaging modalities and specific histopathological markers (Kok et al., 2015). The aim of the current study is to work towards a categorized international consensus based on the diagnostic techniques for CUP. Standardisation of diagnostic approaches will enable the international comparison of incidence, treatment, and survival rates of CUP patients. This in turn will facilitate research and ultimately improve treatment and survival of CUP patients worldwide.

2. Methods

2.1. Identification of existing guidelines

A literature search on CUP guidelines was conducted in the PubMed database with the following search strings: “cancer of unknown primary” AND/OR “CUP” AND ”guidelines” AND/OR “diagnostics”. The search was based on keywords (MeSH) and free text terms. All peer-reviewed English-language guidelines/studies published between 2010 and 2021 were included. Titles and abstracts were used for filtering reviews and research articles. Those considered irrelevant (out of scope) were removed. If the title and abstract did not contain enough information, full-text papers were retrieved and screened. Of the selected articles, reference lists were screened for additional information not found via the database search. In addition, a Google search on English written CUP guidelines was performed, to include those guidelines not found through PubMed. Altogether, the identified guidelines resulting from the literature search were utilized for Delphi survey development.

2.2. Modified Delphi approach

The Delphi approach was used as this is a systematic process for developing and measuring consensus among participants regarding a certain topic (Jones and Hunter, 1995; Humphrey-Murto et al., 2017). By using the Delphi method, undue dominance by specific individuals would be prevented by providing anonymity among the available methods for building consensus (Humphrey-Murto et al., 2020). The current study consisted of four sequential surveys containing agree/-disagree questions and multiple-choice questions. The results from every survey served as input for the questions in the subsequent survey, a method referred to as Daisy chaining. The cut-off value for consensus was set at 70 % or higher, based on medical Delphi studies found in the literature (Haddad et al., 2021; O’Donnell et al., 2020; Smits et al., 2020; Ralph et al., 2020). The study was not subject to the Dutch Medical Research Involving Human Subjects Act (WMO code 2020.0743), and therefore no further ethical approval was required. If desired, the original surveys will be provided upon request.

2.3. Expert panel

Participants were identified based on (co-) authorship of CUP literature, contributions to CUP guidelines, research in the field of CUP, or treatment of CUP patients. Experts included medical specialists, data managers of cancer registries, and researchers. Participants were recruited via CUP organizations, research networks, and suggestions from other experts. We aimed on an equal international distribution of participants. All the invitations including informed consent were completed by email. Upon no response, two reminders and one final email were sent. All participants had the option to withdraw from the study throughout the project.

2.4. Data collection

An initial survey was developed based on the ESMO, NICE, NCCN, and SEOM guidelines (Fizazi et al., 2015a; Ettinger, et al., 2021; Excellence, 2010; Losa et al., 2018a). Data on the opinion of the expert panel was collected through four Delphi surveys, that were disseminated between March 2021 and June 2021 (Young and Hogben, 1978). The first survey aimed at evaluating the overall opinion on CUP diagnostics. The second- and third survey respectively aimed at definition of a set of initial diagnostics before the diagnosis of CUP could be made, and a set of advanced CUP diagnostics, with the fourth survey being a roundup survey. All surveys contained ten to twelve questions, and were checked by a communication strategist to allow for the impartial design of the study. The results of each Delphi survey were shared with the panel in the form of a graphical summary. To enhance the response rate in the different rounds, reminders were sent after two weeks of the initial email containing the survey.

2.5. Data analyses

Answers and comments were exported into an Excel spreadsheet, and a coding file was developed to guarantee anonymity and facilitate analyses. Every agree/disagree question was individually analysed by considering the percentage of (dis)agreement and the comments given. Agree/disagree questions that did not achieve consensus were reformulated ($\geq$ 40 % consensus), or left out for the next round ($<$ 40 % consensus). For the multiple-choice questions, agreement was defined by examining the percentage of the panel rating the individual elements. Based on comments, elements rated less than 70 % were either rephrased or left out of the subsequent survey. Elements of the multiple-choice questions and agree/disagree questions that reached consensus, were included in the subsequent survey and reformulated based on comments given to obtain more information.

3. Findings

3.1. Literature study

The literature study identified the diagnostic CUP guidelines of ESMO, NICE, NCCN, and SEOM (Fizazi et al., 2015a; Ettinger et al., 2021; Excellence, 2010; Losa et al., 2018a). The initial diagnostic approach of these guidelines was compared in Supplementary Table 1 and the details on initial and advanced diagnostics in the various guidelines are mentioned in Supplementary table 2. Overall, the guidelines recommended conducting a comprehensive history and physical examination, a CT-scan of either thorax, and/or abdomen, and/or pelvis, and routine laboratory tests. The main differences in the recommendations concerned a mammography, an MRI, and a PET/CT scan. None of the guidelines recommended targeted gene panels or whole genome sequencing.

3.2. Expert panel

A total of 90 CUP experts were invited by email to participate in the Delphi study. A total of 37 participants responded positively, 37 participants did not respond, and 16 participants did not want to participate (response rate 59 %). Participants came from 15 different countries divided over four continents and had a multidisciplinary background. The first survey was completed by 37 participants, the second survey by 36 participants, and the third and fourth survey by 34 participants. For every survey round, the profession and nationality of the experts are depicted in Supplementary table 3.

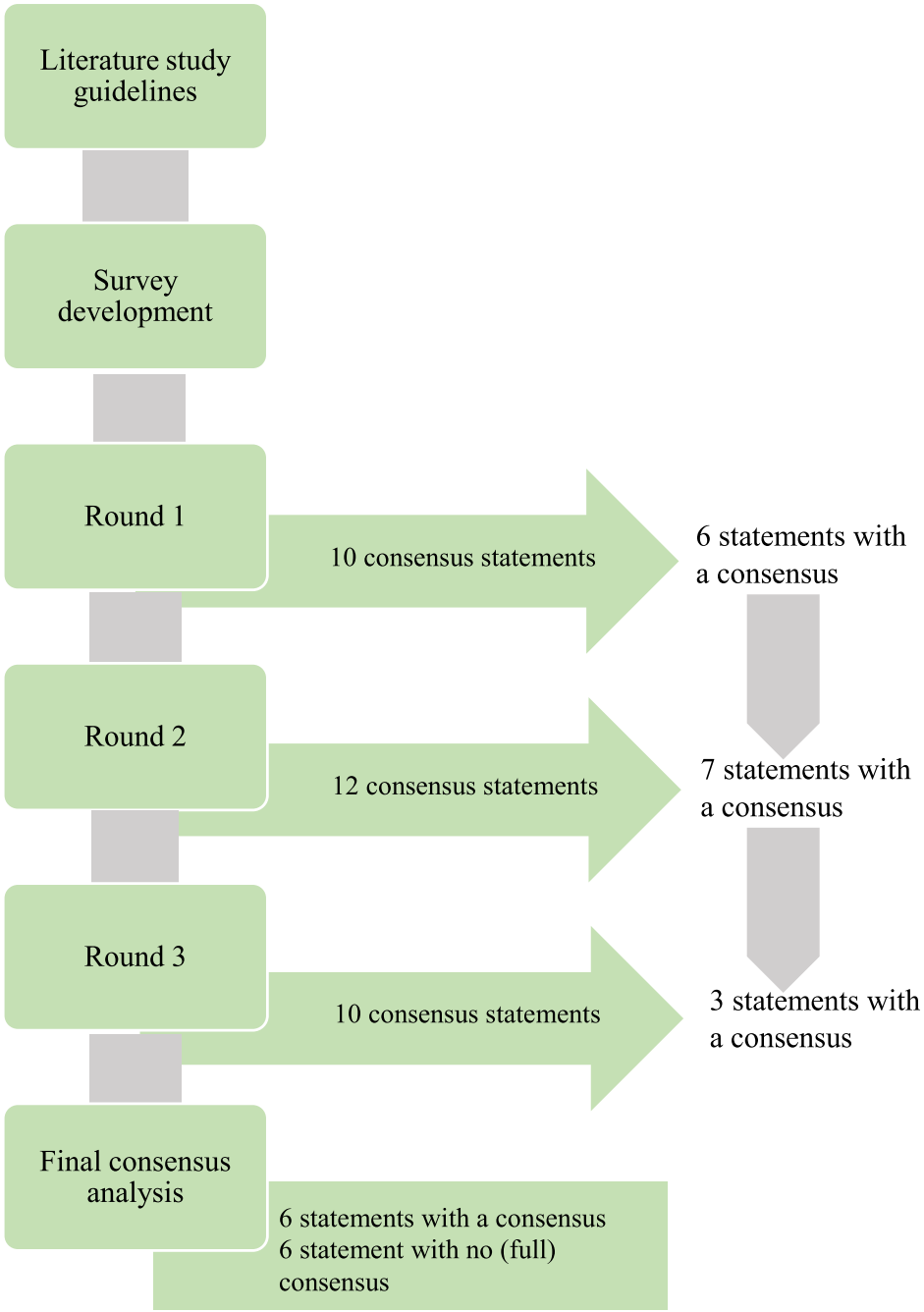

Fig. 1. Modified Delphi consensus format. The study consisted of four survey-rounds. A total of 22 statements achieved a consensus and 22 did not.

3.3. Delphi study

Out of 37 experts who started the study, 34 completed all four rounds of the Delphi consensus process. The results are depicted in a flowchart outlining the survey process, see Fig. 1. A total of 22 statements reached a consensus, while 21 did not. The panellists received a total of four surveys that contained questions on the following topics: organization, symptom-based examination, diagnostic imaging, and pathology. The consensus-rate for statements that reached consensus and statements that did not reach consensus is presented in Table 1 and Table 2, respectively. Most consensus was found on the topic of organization, while the symptom-based examination and pathology appeared to be topics that remain under discussion.

3.4. General outcomes

Performance status should be taken into consideration when planning diagnostic workup. The final diagnosis of CUP should be made by a multidisciplinary team, that should at least consist of a medical oncologist, a pathologist, and a radiologist. The panel agreed there should be an intended maximal time between first hospital visit and diagnosis of CUP, with 8–14 days most answered (39 %). The panel agreed that the C in CUP stands for cancer and not for carcinoma, as often is suggested.

3.5. Proposed diagnostic workup CUP category 0 and 1 (initial)

Consensus was reached on a multi-layer classification for CUP patients. Based on the outcomes of the Delphi study, a diagnostic workup strategy (Fig. 2) with four categories (0−3) was proposed for CUP. Patients who did not undergo any diagnostics were categorized as CUP Category 0. The panel agreed upon the diagnostic techniques for category 1, which should include a comprehensive history and symptom-based physical examination, a symptom-guided CT scan (neck, chest, abdomen, and/or pelvis), a symptom-guided endoscopy or ultrasound, a biopsy of the most accessible lesion, and an analysis of full blood count and gender specific serum tumour markers. Although no consensus was reached on which serum tumour markers specifically, the majority agreed to test at least prostate-specific antigen, human chorionic gonadotropin, cancer antigen-125, and alpha fetoprotein. According to the panellists, immunohistochemistry (IHC)-testing on biopsy material of the most accessible lesion is part of the initial diagnostic workup of CUP category 1 patients.

3.6. Proposed diagnostic workup CUP category 2 and 3

The diagnostic techniques for category 2 (supplementary) and 3 (advanced) appeared to be topic for more discussion compared to the diagnostic techniques identified for category 1. The panellists agreed upon the fact that the locations of the metastases should guide the diagnostic strategy regarding supplementary and advanced diagnostics. The exact category of a symptom-guided MRI or ultrasound, a PET/CT scan, additional IHC testing on the biopsies, targeted gene panels, and whole genome sequencing within the diagnostic workup (supplementary or advanced) remained under debate.

4. Discussion

In this modified Delphi study, 34 international panelists reached a consensus on a multi-layer CUP diagnostic workup procedure, organization of the multidisciplinary team, necessary diagnostic techniques for the first layer of the strategy, and presence of an intended timeline for diagnosis. While the panelists did not reach a complete consensus on supplementary and advanced diagnostic procedures, this study is still a significant first action and a steady base towards an international consensus.

The 81 % agreement of panelists on having a tiered system to

Table 1
Statements that reached consensus. The consensus rate(%), the amount of comments and the general topic of given topics are depicted.

Statements	Agreement (%)	Comments (N)	General Comments
Organization			
The C in CUP should stand for cancer	85	11	• Limiting C to carcinoma is not convenient
A tiered system would be helpful and informative regarding global comparison of CUP incidence and survival data.	81	14	• Helps to standardize the diagnosis
There should be an intended maximal time between first hospital visit and diagnosis of CUP.	70	26	• Depends on the necessary investigations • 2–4 weeks • As soon as possible
Distribution pattern of metastases in a CUP patient is helpful in comparing incidence and survival rates between countries.	74	9	• Only if guidelines are harmonized
The diagnosis of CUP should be made by a multidisciplinary CUP team.	86	12	• Ultimate diagnosis should be a team decision • MDT consisting of at least an oncologist and a pathologist
A multidisciplinary CUP team should consist of at least an oncologist, a pathologist, and a radiologist.	89	8	• The three are core in the diagnosis and management of cancer patients
A multidisciplinary (CUP) team should be the one to proceed the initial diagnostic workup, when no primary tumour is found.	93	5	• First workup will be done by any medical center / professional • CUP MDT should not be for general diagnostics
Performance status should be taken into consideration when planning diagnostic workup.	73	12	• Should always be taken into account
Symptom-based examination			
A comprehensive history and symptom-based physical examination, including breast, nodal areas, skin, genital, rectal and pelvic examination should be part of minimal CUP diagnostics.	83	10	• Should be done by the referring physician. • Important to get complete picture
A biopsy of the most accessible metastatic lesion should be part of a set of minimal CUP diagnostics.	97	7	• Essential initial step in cancer diagnosis
A comprehensive history and symptom-based physical examination should ideally be part of an initial diagnostic workup.	100	1	• These should precede investigations
Describing the number and location of lesions (based upon the conducted CT scan) should be part of an	97	2	• Only relevant after CUP diagnosis

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Table 1 (*continued*)

Statements	Agreement (%)	Comments (N)	General Comments
initial diagnostic workup.			• Standardized reporting is more important
Analysing full blood count and (gender specific) blood markers should ideally be part of an initial diagnostic workup.	88	9	• What is gender specific? • Most biomarkers don't have predictive value
Diagnostic imaging			
A CT scan should at least have been conducted before diagnosing a patient with CUP.	70	21	• High dose CT of neck + chest + abdomen
A symptom-guided CT scan should be part of a set of minimal CUP diagnostics.	83	9	• Should always be part. Not only symptom-guided. • Crucial part of diagnosis
A symptom-directed scopy or ultrasound should be part of a set of minimal CUP diagnostics.	75	12	• Only if symptoms point to these areas
A symptom-based CT (neck/chest/abdomen/pelvis) should ideally be part of an initial diagnostic workup.	94	4	• CT of the chest abdomen pelvis should always be part of the initial workup • Symptoms should not dictate the imaging
Determining the number of organs with metastatic lesions should be included in the minimal CUP diagnostics.	81	9	• Can provide clues about the possible original primary site
Morphology-type (adenocarcinoma, sarcoma e.g.) should determine the course of the advanced CUP diagnostics.	83	8	• Can often be identified by IHC
Pathology			
The location(s) of organs with metastases should determine the course of advanced diagnostics.	91	13	• Both the location and the amount of organs • Will not solve CUP diagnosis but contribute to overall info
A selection of histopathological markers should have been assessed before diagnosing a patient with CUP.	95	12	• Crucial part of diagnosis
The choice of IHC markers should be appropriate and broad enough to differentiate between epithelial and non-epithelial malignancies.	77	21	• Cytokeratin's (CK), vimentin and S100′ • Can be used for more than differentiation between epithelial and non-epithelial markers

facilitate international comparison of CUP incidence and survival data lead to the proposal of a diagnostic workup strategy. The proposed layers of the system are based on the surveys and comments of the panelists, besides an extensive literature research. One of the key components of a multi-tiered system is the presence of tiers of evidence-based interventions tailored for patients that can be adjusted according to the results from diagnostic examinations. These help to

Table 2
Statements that did not reach consensus. The consensus rate (%), the amount of comments and the general topic of given topics are depicted.

Statements	Agreement (%)	Comments (N)	General comments
Organization			
What should be the intended maximal time between first hospital visit and conclusion of a minimal set of CUP diagnostics?		13	• Depends on the minimal set • 2 weeks is ideal, 4 weeks is realistic
8–14 days	38		
15–21 days	14		
22–28 days	24		
A CUP MDT minimally consists of an oncologist, a pathologist, and a radiologist. If possible, the MDT also includes a nuclear medicine specialist and a surgeon.	56	12	• The core three is enough • Too many team members is a disadvantage • Others can be consulted as necessary
Symptom-based examination			
Which physical examinations should at least have been addressed before giving the diagnosis CUP?		16	• Physical examination based upon complaints • Depending on location of involved nodes and histopathology
Neck	68		
Breast	65		
Head	62		
A biopsy is invasive and therefore the aim should be to take only one biopsy of the most accessible lesion during the diagnostic workup.	50	17	• A single biopsy is close to nothing • More biopsies can provide more information
If a biopsy of the most accessible lesion did not identify the primary tumour, then a liquid biopsy (blood sample) is preferred in CUP diagnostics.		14	• May identify targetable lesions • Is not/less helpful in identifying the primary • Still experimental, not FDA approved
Agree; minimal CUP diagnostics	12		
Agree; advanced CUP diagnostics	52		
Disagree	36		
One or more biopsies of the most accessible lesion(s) should ideally be part of a supplementary diagnostic workup.		6	• Multiple biopsies in a single visit • This is mandatory • 1 biopsy is not really enough anymore
Agree	34		
Disagree; should be part of initial diagnostic workup	51		
Disagree	14		
The amount of organs with metastases should determine the course of advanced diagnostics.	47	10	• Pattern not number • Amount of tumour/bulk is important
The number of involved organs in a CUP patient is helpful in comparing incidence and survival rates between countries.	68	13	• Probably helpful in selected cases • Will have no overall value
Diagnostic imaging			
A symptom-directed X-ray should be part of a set of	44	14	• Too low specificity and sensitivity

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Table 2 (*continued*)

Statements	Agreement (%)	Comments (N)	General comments
minimal CUP diagnostics.			• If a CT is performed, an X-ray might be superfluous
If a CT is not available, an X-ray of thorax and abdomen is preferred over a symptom-directed X-ray.	47	18	• Not useful in detecting tumour • Diagnosis of CUP without a CT is unacceptable
A symptom-guided ultrasound **or** MRI should ideally be part of a supplementary diagnostic workup.		8	• US: easy, available, cheap, and directs biopsies • MRI: less available and more expensive
Agree	42		
\Disagree; should be part of initial diagnostic workup	26 17		
Disagree; should be part of advanced diagnostic workup	15		
Disagree			
A symptom-guided scopy should ideally be part of a supplementary diagnostic workup.		9	• Avoid any futile invasive procedures • Depending on findings from initial diagnostic workup
Agree	47		
Disagree; should be part of initial diagnostic workup	29 15		
Disagree; should be part of advanced diagnostic workup	9		
Disagree			
A PET/CT scan (tracer independent) should be part of a supplementary diagnostic workup.		11	• Use PET only when standard tools fail • Not necessary after CT
Agree	41		
Disagree; should be part of initial diagnostic workup	15 29		
Disagree; should be part of advanced diagnostic workup	15		
Disagree			
Pathology			
Regardless of morphology-type, how many immunohistochemical markers should have minimally been assessed in tissue in a set of minimal CUP diagnostics?		21	• One-size-fits-all is difficult. • The number depends on clinicopathologic features • Number will not be interesting, but what kind of marker is
6–10	32		
Unanswered	32		
Other	13		
Next generation sequencing (NGS) methods should be part of the diagnostic tools of CUP.	58	19	• Most centers lack the modern molecular techniques such as NGS and personnel • Can guide further diagnostic procedures
Molecular analysis of DNA or RNA should be part of a set of minimal CUP diagnostics.	56	17	• Would limit the ability to collect data internationally • Does not deliver a differential diagnosis on its own
Which biopsies should at least have been addressed before giving the diagnosis CUP?		30	• Biopsy of at least one metastatic sit • Any site suspicious for a primary tumour
Other	70		
Lymph node biopsy	24		
• Other: PSA, beta-HCG, AFP, CEA • important to complement the evaluation of the patient	Which serum levels should at least have been assessed before giving the diagnosis CUP? Full blood count Liver function tests Lactate	16 62 57 51	
• Tumour markers depending on sex, age, location			
Full blood count and blood markers PSA/ER, CA125, h-CG, and AFP should all be part of a basic set of minimal CUP diagnostic work-up.	67	16	• PSA is hardly relevant for females • Tumour markers only in specific situations
Whole genome sequencing should ideally be part of an advanced diagnostic workup.		16	• Can be useful • Targeted sequencing is sufficient and WGS not necessary
Agree	50		
Disagree; should be part of supplementary diagnostic workup	35 15		
Disagree			
Targeted gene panels should ideally be part of an advanced diagnostic workup.		12	• Not diagnostic • May have therapeutic benefits
Agree	50		
Disagree; should be part of supplementary diagnostic workup	23 27		
Disagree			

standardize the diagnosis. The multi-tiered pyramid was initially introduced to school teachers in 1996 (Walker et al., 1996). This systemic, continuously improving framework in which data-based problem-solving and decision making is implemented, has been introduced in the medical domain and is practiced across all classes of the diagnostic systems to deliver interventions for improving outcomes (Averill et al., 2011; Dong et al., 2020).

The initial workup was uniformly agreed upon by our panelists, which is in line with existing guidelines. However, some statements did not reach an agreement, such as an extended CUP MDT (besides an oncologist, pathologist, and radiologist, also involvement of a nuclear medicine specialist and a surgeon). An expert reasoned that the core three MDT is enough, and too many team members can be a disadvantage. On the other hand, NICE recommends that a CUP team should at least include a palliative care physician and a CUP specialist nurse or key worker as a minimum. SEOM recommends that for the tissue sampling a multidisciplinary collaboration with pathologists and surgeons is crucial, while ESMO indicates the especially favorable-risk CUP patients may benefit from multidisciplinary management as they are being

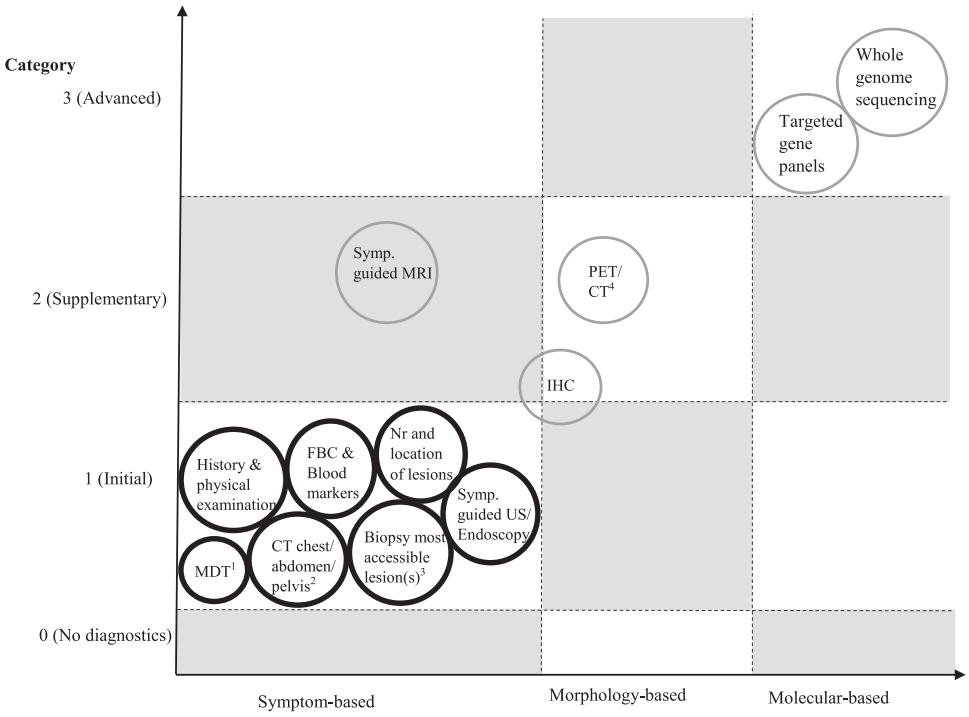

Fig. 2. Proposed diagnostic workup strategy for CUP. The workup is divided into four categories (0−3). In black are the diagnostic techniques that reached consensus. In gray are the diagnostic techniques that were agreed to be in the workup strategy, however the exact layer remains under debate. Disclaimer: for every step in this scheme, performance status (including evaluation of serum levels) of the patient should be taken into consideration. 1: MDT consists of at least an oncologist, a pathologist, and a radiologist. 2: If CT-scan not available, a symptom-based X-ray is preferred. 3: Wherever that may be performed safely. 4: Tracer-independent. FBC = full blood count; Nr = number.

recognized and subsequently being treated (Fizazi et al., 2015b; Losa et al., 2018b). Given the increasing importance of molecular diagnostics in CUP assessment, addition of a molecular biologist to the team seems a logical next step.

As the time is against CUP patients regarding the diagnostic lead-time to identify the primary tumor site, fast diagnostic pathways and an intended time-frame are required. Although it is poorly discussed in the existing guidelines and our panelists did not reach a consensus for the exact number of days, it is essential to have a maximum intended time between first hospital visit and diagnosis. One of our panelists reasoned that two-weeks is ideal for patients with CUP and four-weeks is realistic. Comparably, national health service UK (NHS) mentions that outpatients with CUP should be referred to the CUP team immediately, using the rapid referral pathway for cancer, which is assessing them within two weeks of referral, and time line for assessing in-patients with CUP is one working day after referral (Anon,n.d.).

Imaging could play an integral role in the multidisciplinary diagnostic evaluation of patients with CUP (Sheibani et al., 2013). To our surprise, only 42 % of the respondents agreed on mammography as initial diagnostic imaging technique. As a consequence, mammography was not included as initial diagnostic technique within the categorized model. Experts commented that a CT-scan is preferred over mammography as well as X-ray. CT is the most repeatedly utilized imaging modality for managing CUP, and PET scan is valuable for the diagnosis, staging, and re-staging of many malignancies. Therefore, many studies evaluated the sensitivity, specificity, and detection rate of the primary tumor in patients with CUP, employing PET/CT scans. Recent investigations demonstrate a higher success rate of PET/CT in the detection of origin from 66 % to 87 %, with up to one-third of the patients undergoing successive transformations in management strategy due to determining the primary tumor (Thapa et al., 2018; Yu et al., 2016a). PET/CT scan accurately detected the primary carcinoma of 115 patients in a large study that included 449 patients, and this inspires utilizing PET/CT in earlier diagnostic phases of patients (Yu et al., 2016b).

Some of the pitfalls of 18 F-FDG PET/CT are its false-positive results in some cases and its poor sensitivity for detecting small tumors (50 %), as primary tumors from patients that were suspected of CUP are in some cases smaller than 1 cm (Chu et al., 2010). Therefore, PET/CT scans are optional in some guidelines, or placed in advanced categories after appropriate more invasive investigations (including endoscopy and targeted excision biopsies) did not result in a primary tumor (Fizazi et al., 2015b; Losa et al., 2018b). Meanwhile, our panelists also consider PET/CT scans as a supplementary diagnostic workup (category-2). Moreover, despite the statistics suggesting that PET/CT is a better tool for identifying the origin of cancer than MRI (22–44 % vs. 20–27 %), there are still some disadvantages, such as poor sensitivity for smaller lesions, the considerable number of false-positive and false-negative findings, and the not verified cost-effectiveness of utilizing it as standard-of-care (Thapa et al., 2018; Tomuleasa et al., 2017). Thus, more studies are required to assess the survival rates after implementing PET/CT for CUP workup.

Immunohistochemistry (IHC) should be carried out in all CUP patients according to the available guidelines. Our panelists agree that histological tumor type (e.g. adenocarcinoma, squamous cell carcinoma, etc) should guide the course of the advanced CUP diagnosis, and that IHC markers should be appropriate and broad enough to differentiate between several epithelial and non-epithelial malignancies. Pathology diagnosis employs histological tumor typing as the first clue; if morphology is unclear, IHC might help to figure out the tumor lineage (De Young and Wick, 2000, August). However, if the tumor also lacks lineage differentiation, the pathologists cannot indicate a decisive diagnosis. In this study unfortunately, it was not possible to identify the exact immunohistological markers in detail among the proposed categorized model. To overcome this challenge, modern techniques such as gene expression profiling and next-generation sequencing have been suggested to discover the tissue of origin (Rassy and Pavlidis, 2020).

More contemporary techniques are available to unravel the genomic profile of tumors as well as the identification of so-called ‘druggable’ targets. By using data derived from tissue sequencing and by comparing the outcomes to available databases, like the cancer genome atlas (TCGA), it seems to be possible to predict the tissue of origin (Weinstein et al., 2013). The possibility to predict the tissue of origin in a fairly high percentage of patients has been shown by Jiao et al (Jiao et al., 2020). Next generation sequencing (NGS) using targeted gene panels or whole-genome sequencing (WGS) may be fitted in advanced diagnostic workup (category-3). Some panelists commented that the outcomes of

targeted gene panels lead to alternative treatment options. In addition, there was an argument that WGS is not necessary and targeted sequencing should be sufficient. The use of signature analysis based on sequencing data has some limitations, such as the difficulty to differentiate between cancer types because of overlapping profiles. In addition, some of the more rare cancer types are not captured well enough in databases like TCGA. Therefore, the clinical benefit of trials such as TAPUR (Targeted Agent and Profiling Utilization Registry), NCT-MASTER (Molecularly Aided Stratification for Tumor Eradication), and CUPISCO trial (Cancer Immunotherapy Versus Platinum-Based Chemotherapy) are yet to be determined, as the outcomes data are not currently available to recommend routine use of molecular profiling for CUP workup (Mangat et al., 2018; Lier et al., 2018; Pauli et al., 2021). The value of molecular profiling still needs to be validated in larger studies, for example in meta-consensus initiatives (Hardman et al., 2022). In addition, clinical impact in terms of survival rate is yet to be measured. Moreover, it has to be unraveled whether the use of genome, transcriptome, methylome, or a multi-omic approach is optimal. Several initiatives worldwide have been studied the past years and are still ongoing to evaluate on this topic (Bagge et al., 2018; Bavafaye Haghighi et al., 2019; Zhao et al., 2020; Kang et al., 2021; Boussios et al., 2021).

An advantage of this study is the diversity of experts and their professional backgrounds, allowing for different perspectives on the availability of diagnostic techniques internationally. Additionally, the involvement of external third parties in survey development allowed for the impartial design of the study. The option of further specification of the expert's arguments allowed us to enhance subsequent surveys. Limitations of this study are perhaps a biased expert panel due to the limited number of experts in CUP, the covid-19 pandemic, and logistic problems with emails outside of our control. Furthermore, there was a clear bias towards experts from high-income countries. Although experts from low-income countries, from multiple continents, with less high-tech health care possibilities were invited, no response was received even after multiple reminders. In addition, over time, guidelines are updated to standards of that time, including more advanced diagnostics and site specific assessments. Diagnostics such as microsatellite instability testing, tumor mutational burden testing, and the consideration of NGS testing were not included in the surveys of the current study, and should be topic of debate in future consensus discussions regarding site specific and/or advanced CUP diagnostics.

In conclusion, a consensus was reached on a multi-layer workup strategy for CUP, on the diagnostics for initial diagnostic workup, and on an intended time frame for the diagnostic trajectory. Implementation of the diagnostic techniques of CUP category-1 will enable the international comparison of patients regarding treatment and survival. This will facilitate future studies, consensus on the multi-layer workup strategy, and ultimately improvement of patient healthcare. Consensus regarding CUP category-2 and category-3 should be further discussed in detail in the nearby future, with special focus on the use of IHC marker types.

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CRediT authorship contribution statement

Iris van der Strate: Formal analysis, Data curation, Visualization, Writing – original draft. **Fatemeh Kazemzadeh:** Visualization, Writing – original draft, rewriting & editing. **Iris D. Nagtegaal:** Supervision, Investigation, Writing – review & editing. **Debbie Robbrecht:** review & editing. **Agnes van de Wouw:** review & editing. **Catarina S. Padilla:** Writing – review & editing. **Saskia Duijts:** Supervision. **Manel Esteller:** review & editing. **F. Anthony Greco:** review & editing. **Nicholas Pavlidis:** review & editing. **Amir Qaseem:** review & editing. **Petur Snaebjornsson:** review & editing. **Sophie Veldhuijzen van Zanten:** Writing – review & editing. **Caroline Loef:** Supervision, Conceptualization, Investigation, Project administration, Writing – review & editing.

Conflict of interest statements

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

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Appendix A. Supporting information

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