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Original Article

Best-Practice Biomarker Testing of Oesophago-Gastric Cancer in the UK: Expert Consensus Recommendations Developed Using a Modified Delphi

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Abstract

Aims: Oesophago-gastric cancers (OGCs) are amongst the most commonly diagnosed malignancies worldwide and are associated with high disease-related mortality. Predictive biomarkers are molecules that can be objectively measured and used to indicate a likely response to therapeutic intervention, thus facilitating individualised cancer therapy. However, there remains variation in uptake and implementation of biomarker testing across the UK.
Materials and methods: We conducted a modified Delphi study to formulate consensus recommendations for best-practice biomarker testing of OGC in the UK. We employed two rounds of online questionnaires followed by a virtual consensus meeting. Biomarkers for discussion included HER2, MSI/MMR, and PD-L1. Topics comprised the overall biomarker pathway, pre-analytical, analytical, and post-analytical considerations, including challenges in current practice.
Results: Twenty-six and eighteen participants completed the first and second round Delphi questionnaire, respectively, with an even split of pathologists and oncologists from across the UK. There was consensus (>80% agreement) across several topics, including the requirements for standardisation of the pathway, which must include coordination throughout the tissue journey, requirements for a quality-assured process to ensure accuracy and validity of testing, plus the need for clear, detailed information on the pathology report to support treatment decisions. There was consensus amongst oncologists regarding reflex testing of all biomarkers depending on histology; however, concerns over capacity in relation to workload and availability of pathologists were evident among the pathologists. Overall, participants were in the opinion that reflex testing improves the speed of treatment decisions and improves patient care.
Conclusion: The recommendations reflect best-practices and should be implemented to support rapid multidisciplinary team decision-making within oesophago-gastric cancer. Results reflect the need for standardisation and demonstrate the challenges faced in clinical practice by those requesting and testing biomarkers for oesophago-gastric cancer, suggesting significant concerns relating to pathologist capacity.

Keywords: Consensus recommendations; HER2; MSI/MMR; oesophago-gastric cancer; pathology; PD-L1

Introduction

Oesophago-gastric cancers (OGCs), including gastric cancer, oesophageal cancer, and gastroesophageal junction cancer (GOJ), are amongst the most commonly diagnosed malignancies worldwide and are associated with high disease-related mortality [1,2]. Globally, approximately 769,000 and 545,000 deaths were due to gastric and

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oesophageal cancer, respectively in 2020 [2]. In the UK, approximately 11,000 people are affected each year [3]. Patients are frequently asymptomatic during the early stages; therefore, diagnosis is often at an advanced stage [2,4], with approximately one third of patients presenting with metastatic disease [5]. Despite improvements in survival, patient outcomes are poor and prognoses unsatisfactory, with high incidence of recurrence after surgery [6].

Biomarkers are biological molecules that can be objectively measured and used to indicate normal biological processes, abnormal changes or likely response to therapeutic intervention [6,7]. Advancements in molecular profiling have improved care for people with OGC, enabling a change from standard chemotherapy to targeted therapy options [7], facilitating individualised treatment [2,8]. Established, validated, predictive biomarkers include human epidermal growth factor receptor 2 (HER2), microsatellite instability or deficient mismatch repair (MSI/dMMR), and programmed death ligand 1 (PD-L1). Evaluating the status of these biomarkers is recommended within treatment guidelines, based on published evidence that demonstrates how therapy may be directed according to biomarker expression to influence response rates and outcomes in people with OGC [9–11]. However, due to lack of clear guidance, there is variation in practice for biomarker testing. Additionally, across the UK there is variation in facilities and implementation, often depending on local funding and resources [12], potentially resulting in delays to appropriate treatment for patients. Variation may be evident at pre-analytical, analytical, or post-analytical stages in the process, thus there remains a need for a best-practice framework for biomarker testing in OGC to improve patient care.

Objective

To develop expert consensus recommendations for best-practice biomarker testing for OGC in the UK.

Methods

To formulate consensus recommendations, we conducted a modified Delphi study; an accepted, robust approach for obtaining consensus, often used within the healthcare setting where there is insufficient or conflicting evidence [13–16]. We followed ACCORD guidance for reporting consensus studies [17]. Prior to study initiation, a steering committee was convened, including clinical experts from pathology and oncology. The steering committee were selected from diverse UK regions and are considered experts in their field. An overview of the process is provided in Figure 1.

Delphi participants

To be eligible, participants were required to be a pathologist, oncologist, or gastroenterologist practising in OGC in the UK. Potential participants were identified from relevant literature and a targeted search. Additionally, members of the national gastro-intestinal pathology external quality assurance team (EQA) were invited to participate, alongside those on the study sponsor's internal database who had indicated their interest in research participation. Individuals did not receive remuneration for completing the Delphi questionnaires. Additionally, three individuals from different treatment centres were invited to be panellists in the consensus meeting, acting as a validation stage.

Potential participants received an invite email with a link to the Delphi questionnaire (hosted on the 'SmartSurvey' platform (https://www.smartsurvey.co.uk)). Participants were provided with instructions for completion, provided informed consent, and were made aware that their participation was voluntary, that their responses were anonymous in relation to other participants and to the study sponsor, and that they could withdraw at any time.

Online questionnaires

To inform the development of statements for the first round, a non-systematic pragmatic literature review was conducted to identify relevant articles, guidelines and commentaries. A keyword free-text search was carried out, including search terms such as 'biomarkers', 'molecular testing', 'oesophago-gastric cancer', and 'upper gastrointestinal cancer'. Snowball searching of relevant studies was conducted to ensure comprehensive capture of publications. Using the publications identified (Supplementary file 1), statements were drafted, undergoing several rounds of revision by the steering committee.

The first round Delphi consisted of 51 questions/statements categorised into participant information, biomarker pathway, pre-analytical, analytical and post-analytical (Supplementary file 2).

Where appropriate, some statements, for example, those relating to laboratory procedures, were directed solely towards pathologists. Participants were asked to rate each statement based on their own opinion in relation to guidance and current practice. Each statement was rated using a 7-point Likert scale where 1–3 represented 'strongly disagree', 'disagree', 'somewhat disagree', 4 represented 'neither agree nor disagree' and 5 to 7 represented 'somewhat agree', 'agree' and 'strongly agree'. There was also an option to state they did not have sufficient knowledge to provide a rating, and there was free-text space where participants were encouraged to provide further explanation.

Following completion, responses were consolidated and analysed to quantify levels of agreement. Whilst there is no agreed definition on consensus levels, previous studies have used between 50% and 97% [16,18], with 80% being deemed to represent a high level of consensus amongst participants [19]. Therefore, a pre-determined level of $\geq$80% agreement was considered to demonstrate good consensus; $\geq$60 to $<$80% some consensus and $<$60% poor consensus. Levels of agreement were calculated overall and according to profession (pathologists and oncologists). Following analysis of the first-round statements, those with $<$80% agreement

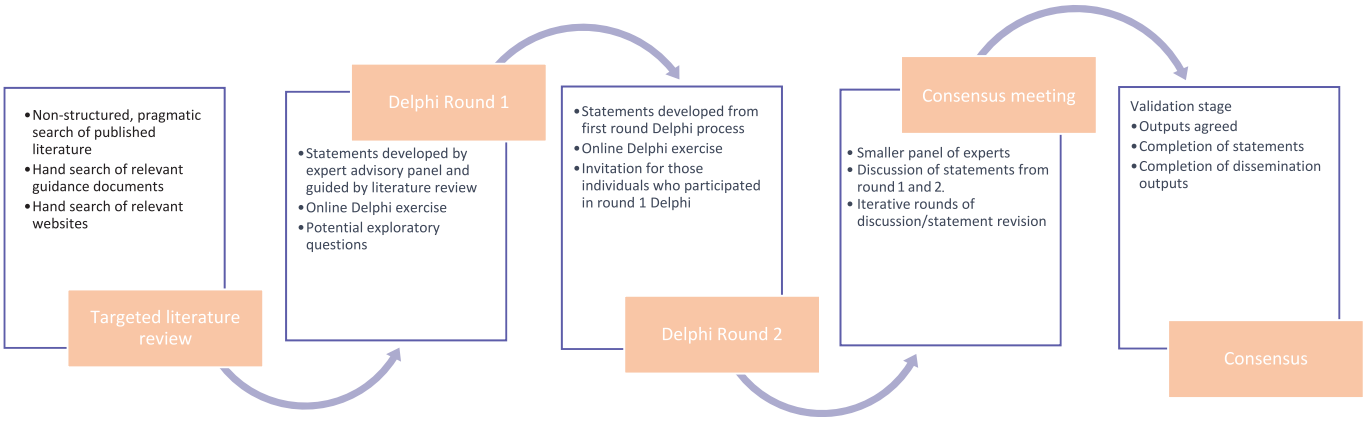

Fig. 1. Overview of the modified Delphi approach.

were re-drafted for the second round based on the comments left by participants.

Only those participants who had completed the first round were invited to participate in the second round, which followed the same topics as the first round; however, included only 30 questions/statements. The procedure for completion and analysis mirrored that for the first round. Participants were informed that statements were redrafted based on responses, but no formal feedback was provided to the participants between rounds.

Consensus meeting

Following completion of the Delphi questionnaires, responses from both rounds were consolidated for discussion at an online consensus meeting. During this phase, results were presented, and the panellists considered the comments provided by the Delphi participants to aid understanding where consensus was not achieved. The meeting focused on validation of the findings and agreement for final recommendations. Assumptions were refined by a facilitator who captured discussion and decisions and presented these back for final approval.

Results and discussion

Delphi participants

A total of 108 individuals were invited to participate in the first round of Delphi, conducted from 20th April to 4th May 2023, of which 26 fully completed the questionnaire. The majority of participants (88%) stated that they practiced in a centre that has the facilities to both diagnose and manage OGC. All participants worked within the NHS, with 30% also working within the private setting. Participants represented the UK, covering England (n = 17), Scotland (n = 4), Wales (n = 3), and Northern Ireland (n = 1). One participant did not provide their location. The participants were invited to complete the second round (4th to 15th September 2023); 17 fully completed the questionnaire, and one participant completed 27 of the 29 statements, therefore, their data were also included in the analysis. The participants who completed the second round represented England (n = 11), Scotland (n = 3), and Wales (n = 3); one participant did not provide their location. For both rounds, there was an equal split between oncologists and pathologists.

The formulated best-practice recommendations are presented below (Table 1), followed by a narrative summary of the challenges within clinical practice.

General pathway recommendations

Challenges in current practice

The results demonstrated that, in the majority of cases, healthcare professionals use protocols for biomarker testing and have a good understanding of which tests to request. There was good consensus (89%) that there is a need for standardisation to optimise the biomarker pathway. Although some participants stated they already have a "*streamlined service*", several participants noted concerns in the current biomarker pathway that it can be "*complex*", "*results can come through different routes*", and "*there can be confusion around assays and assessment methods*". The results support the need for clear, consistent guidance and support the development of best-practice recommendations.

There was some consensus regarding the need for a 'tissue coordinator' (78%), with participants agreeing this could "*streamline the service and reduce inequity*" and expressing this should "*be standard of care*". Despite the statement not reaching 80%, comments were largely favourable; panellists agreed there should be a recommendation on coordination, and a designated individual may be beneficial to facilitate this. The key requirement is for coordination in the tissue process, with accountability in place.

To explore current challenges in the biomarker pathway, participants were asked which factors acted as barriers to testing. The most frequently stated barriers included 'limited laboratory capacity', 'limited pathologist capacity', and 'sub-optimal co-ordination between the requestor and

Table 1
Consensus recommendations for best-practice biomarker testing in oesophago-gastric cancer in the UK

General pathway recommendations

Standardised procedures for optimal timing and requesting of relevant biomarker tests and then delivering results to the correct clinician are required across the UK for patients with oesophago-gastric cancer.

Tissue coordination throughout the biomarker pathway must be in place; if local pathways are sub-optimal, having a nominated, existing member of staff to act as a co-ordinator to track the end-to-end tissue journey (from biopsy request to communication of the biomarker result to the multidisciplinary team) will be beneficial to patient care.

Pre-analytical recommendations

The information listed on the biomarker request form should be agreed locally between the trust and the testing laboratory; at a minimum the biomarker request form should include the name of the requesting clinician, the biomarkers to be tested, the histological type of tumour, the site of the tumour, where to send the results (to whom and the correct contact details), and the specimen to be tested (if more than one).

Sufficient laboratory capacity and funding should be in place to accommodate reflex testing of HER2, MSI/MMR, and PD-L1 in oesophago-gastric cancer:

- All patients should be tested for HER2 as soon as gastric cancer is confirmed, regardless of disease stage
- All patients should be tested for HER2 as soon as GOJ cancer is confirmed, regardless of disease stage
- All patients should be tested for HER2 as soon as oesophageal adenocarcinoma is confirmed, regardless of disease stage
- All patients should be tested for MSI/MMR as soon as oesophago-gastric adenocarcinoma is confirmed, regardless of disease stage
- All patients should be tested for PD-L1 as soon as gastric cancer is confirmed, regardless of disease stage
- All patients should be tested for PD-L1 as soon as oesophageal/GOJ adenocarcinoma is confirmed, regardless of disease stage
- All patients should be tested for PD-L1 as soon as oesophageal squamous cell is confirmed, regardless of disease stage

Among patients with oesophageal cancer, PD-L1 should be conducted regardless of histology type (i.e. both patients with adenocarcinoma or squamous cell carcinoma).

Analytical recommendations

Biomarker testing for oesophago-gastric patients should be conducted in an accredited laboratory with rapid turnaround time; they may be in-house or outsourced.

Annual technical external quality assessment (EQA) schemes for biomarkers in oesophago-gastric cancer would facilitate consistent laboratory testing pathways across the UK.

Annual interpretive EQA schemes for biomarkers in oesophago-gastric cancer would facilitate consistent pathologist reporting across the UK.

A minimum of 8 biopsies at endoscopy should be taken to harvest sufficient tumour material for biomarker testing.

It is acceptable to use tissue from a metastatic lesion for biomarker testing of oesophageal-gastric cancers.

Where multiple samples exist, only the most recently acquired sample should be tested for biomarker expression, provided that it meets the minimum testing requirements.

In the absence of a biopsy or resection sample, it is acceptable to use cytology cell block samples where available to test for HER2 and MSI/MMR in oesophago-gastric cancer.

Post-analytical recommendations

Irrespective of where the biomarker testing is conducted (in-house or outsourced) for patients with oesophago-gastric cancer, the biomarker result should be reported within five working days of the request being made.

Once the pathologist has determined the patient's biomarker status, their electronic health record should be updated with the biomarker result(s) within one working day.

The pathology reports for all biomarker tests for oesophago-gastric cancers must be accessible together with the original diagnostic report.

The pathology report, including any biomarker result(s), should be available to all healthcare practitioners in the MDT.

The information listed on the pathology report for biomarker tests for oesophago-gastric cancer should, at a minimum, include the following; patient information, date of test completed, biomarker clone/assay tested, individual responsible for test/authorisation, referring clinician name, block number tested, date of test initiated, whether it is a biopsy or resection specimen, whether the test is UKAS accredited.

Abbreviations: EQA, external quality assessment; GOJ, gastro-esophageal junction cancer; HER2, human epidermal growth factor receptor 2; MDT, multidisciplinary team; MMR, mismatch repair; MSI, microsatellite instability; PD-L1, programmed death ligand 1; UKAS, United Kingdom Accreditation Service.

the pathology laboratory'. The responses reinforced the need for good coordination and highlighted concerns regarding testing capacity. Furthermore, despite several of the participants stating there were no barriers to requesting tests, they noted a lack of funding.

Pre-analytical recommendations

The biomarker request form

Challenges in current practice

Delphi participants were asked what information should be included on the pathology request form; during the consensus meeting, it was agreed that at a minimum, all items that reached ≥60% agreement should be included on the request form (see Table 1.) However, 'biomarker-directed therapy/ies being considered as treatment options and/or related assays' and 'previous treatment' reached less than 60% agreement and during the consensus meeting there was a significant difference in opinion regarding the inclusion of these factors between the oncologists and pathologists. The pathologists stated it was important to have as much information as possible, including an indication of which treatment is being considered. The pathologists stated this was important as there remains uncertainty in validity of using assays not proven equivalent to ones used in published clinical trials, e.g. specific PD-L1 clones. In contrast, the oncologists stated that they may not know

what therapy is planned at the time of requesting the biomarker tests, and therefore this cannot necessarily be completed. Furthermore, the oncologists believed that for PD-L1, any validated assay can be used as is reflected in the drug licencing, and there is some limited evidence that assays are interchangeable [20,21]. Following debate and referral to Delphi participant comments, no consensus was reached. The final recommendation developed states that an agreement should be made locally between the trust and testing facility to ensure coordination in the system. The recommendation reflects the importance of pathologists and oncologists working together and understanding the differing working needs across specialists; the importance of a successful working relationship has previously been noted as crucial to patient care and must be encouraged [22].

Biomarker testing

Challenges in current practice

Delphi participants rated their agreement in relation to conducting HER2, MSI/MMR, and PD-L1 as reflex testing, defined as 'the immediate, pathologist-led initiation of further testing for predictive markers on samples to select therapy without waiting for a multidisciplinary team (MDT) discussion'. Participants demonstrated between 58% and 65% agreement; however, there was an obvious difference between oncologists and pathologists; oncologists agreed that reflex testing should be conducted (>80%), whereas pathologist agreement was typically below 60%. The discrepancy between responses from oncologists and pathologists were considered in relation to the comments provided. The comments from pathologists mirrored those provided as barriers to testing; the steering committee considered the lack of consensus may be due to cost and capacity concerns (for example, comments included "*tests are expensive*", "*at present, I fear this would clog the system*", *"PD-L1 is an expensive test").* To account for these concerns, the statements were redrafted for the second round Delphi to include the prefix 'if sufficient laboratory capacity and funding are in place' (Supplementary material 2).

Considering the high level of consensus provided in the first round Delphi from oncologists, the questions on reflex testing in the second round were only posed to pathologists. The second-round results still did not reach consensus by pathologists for HER2 (67%), MSI/MMR (78%), or PD-L1 (44%), with some participants stating that they believed testing should be limited to those with advanced/metastatic disease or should occur when the patient is reviewed by the MDT/oncologist. Interestingly, the Delphi comments largely remained in relation to capacity; reflex testing can "*be a large resource drain*"; therefore, the panellists believed there was still some misunderstanding that statements are aspirational; acknowledging that recent reports show only 3% of NHS histopathology departments are fully staffed [23]. The comments regarding PD-L1 testing may also reflect a lack of education and awareness about this particular biomarker, likely because it is a newer biomarker that can be considered complex [24]. Furthermore, several antibodies and assays are available for PD-L1 testing, and there remains some variation in opinion as to which specific PD-L1 clones have proven validity, or whether companion diagnostics are required [25]. There was good consensus that PD-L1 testing should be conducted regardless of histology (89%) among pathologists and oncologists.

Despite the lack of overall consensus, the majority of comments from the Delphi participants were in favour of reflex testing for HER2, MSI/MMR, and PD-L1; comments such as "*nearly 50% present with advanced disease and of the remaining, 60% will develop advanced disease within 12*-18 months", "*this is a poor outcome disease and testing needs to be instigated as quickly as possible to maximise likelihood of being able to receive prompt treatment*", *"it also helps limit tissue consumption if all markers are undertaken in one round of cutting"* confirmed the panellist view that the recommendation should be for reflex testing where resources allow. The panellists believed that having results available as early as possible improves patient care. One participant noted that waiting for MDT review before requesting biomarker testing can be detrimental to care: *"this can delay the knowledge of MMR status and therefore delay starting on the best treatment"*. The requirement for an efficient process is also recognised by the recent Welsh guidance for OGC, which states that to reduce turnaround time, all biomarkers should be requested at the same time [26]. To account for any outstanding concerns, the final recommendations state that sufficient laboratory capacity and funding need to be in place to facilitate reflex testing. The recommendations are further supported by the Institute of Cancer Research, who stated that molecular profiling should be offered at point of diagnosis and during treatment, and is critical to ensure that patients can access personalised and effective treatment [12].

Analytical recommendations

Quality assurance of the testing centre

Challenges in current practice

Delphi participants were asked to provide their level of agreement on the statement that 'biomarker testing for OGC patients should be conducted in-house and not outsourced'. The results showed limited agreement (62%), highlighting that the systems in place, rather than location, are important. Comments reflected that either in-house or out-sourcing can be successfully implemented in practice; important factors are speed, efficiency, and accuracy. The re-drafted statement for the second round focused on testing in an accredited laboratory with rapid turnaround times and consensus reached 94%. This recommendation is closely associated with the recommendation for a standardised pathway, including tissue coordination throughout.

In the first round Delphi, pathologist participants were asked about quality assurance schemes. There was a high level of agreement that annual technical quality assessments (92%) and interpretive schemes (85%) should be in place for best-practice testing and reporting, with

participants noting these are "*necessary to guarantee quality*". The results demonstrate that pathologists recognise and agree with published recommendations on quality standards, which ensure accurate and reliable biomarker testing within laboratories [27,28]. The United Kingdom Accreditation Service (UKAS) is the national accreditation body that assesses and accredits medical laboratories; having their accreditation underpins confidence in the quality of outputs [29]. Despite high agreement, published literature suggests there remains a need for education and increased awareness about the necessity of quality assurance [30].

Sample procedures

Challenges in current practice

In the first round of Delphi, there was good consensus on the minimum number of biopsies that should be taken (92%), and 100% agreement that it is acceptable to use tissue from a metastatic lesion for biomarker testing for OGC. Comments demonstrated that it is not necessarily the number that is important, but that sampling depends on "*expertise of the clinician taking the biopsies*" and "*good sampling of unequivocal carcinoma is essential*". This recommendation is consistent with published European guidance, suggesting between five and eight endoscopic biopsies should be harvested for gastric and oesophageal cancer [9,10]. The recommendation is further supported by a UK study that demonstrated that at least eight biopsies should be taken to ensure four to five biopsies with adequate material are available for testing [31].

In the first round of Delphi, there was no consensus (46%) regarding the statement 'where both tissues exist, tissue biopsied at endoscopy and at surgical resection should be tested'; therefore, the statement was reworded to reflect that either can be tested, resulting in 88% agreement. During the consensus meeting the importance of age and stability of samples was discussed. For immunohistochemical biomarkers, it is important that samples are appropriately fixed to prevent technical issues affecting interpretation. Further detailed methodology for histopathological assessment (for example, details on sample preparation, fixation and dissection) can be found in published guidance from the Royal College of Pathologists [32] and from the Association of Upper Gastrointestinal Surgery of Great Britain and Ireland [33].

Delphi participants were asked about the use of cytology samples for HER2 and MSI/MMR expression. Despite this topic not reaching consensus in the first (62%) or second (63%) round, during the consensus meeting, panellists agreed that in the absence of a biopsy or resection sample, a cytology sample is acceptable, as long as there are quality controls in place. Overall, the Delphi participants were cautious about using cytology samples, with concerns over validity. However, availability of tissue samples for molecular analysis can be a challenge; therefore, cytology samples can offer an alternative option [34]. A Delphi participant noted, "*if it is the only tissue then we should test it*"; thus, the recommendation provides an alternative option if no other material is available. Importantly, this only applies to HER2/MMR testing, as PD-L1 testing is not valid on cytology specimens.

Post-analytical

Timing of results

Challenges in current practice

There was good consensus that biomarker results should be reported within five working days (HER2 and PD-LI = 81%, MSI/MMR = 85%), and the health record updated within one day (96%); however, multiple participants commented that these targets are not always feasible, for example: "*is idealistic but not necessarily achievable in the current climate*". Participants were also asked what factors contribute to slow turnaround times: results were similar to the barriers for requesting testing, with 'limited administrative capacity', 'limited pathologist capacity' and 'limited laboratory capacity' the most common responses. It is important to acknowledge that these targets should be deemed the gold standard, and consideration of how these targets can be achieved should be addressed.

Biomarker result form

Challenges in current practice

There was good consensus that biomarker reports should be accessible together with the original diagnostic pathology report and available to all healthcare practitioners within the MDT (96%). When participants were asked which factors to include on the biomarker report, the following factors reached >80% agreement from participants: 'patient information', 'date of test completed', 'biomarker clone/assay tested', 'individual responsible for test/authorisation', 'referring clinician name', 'block number (identifier) tested,' 'date of test initiated'. The remaining two factors, 'whether it is a biopsy (endoscopy sample) or resection specimen', 'whether the test is UKAS accredited' reached between 60% and 80% agreement; therefore, the panellists in the consensus meeting agreed all items should be included as a minimum. The panellists agreed the pathological findings provide valuable information for treatment decisions, thus the report should provide accurate and detailed information; the Royal College of Pathologists in the UK provides examples of structured reports, which can be followed [35], and issues clear guidance on the importance of integrated reporting and the dangers of issuing standalone biomarker reports [36].

Summary of findings

Overall, the recommendations developed support previously published recommendations for improving standards in patient care [12,30,33,35]. Standardisation of the pathway must be coordinated throughout the tissue journey across specialities and include quality-assured processes. Despite concerns regarding overall pathology

capacity, participants were in agreement with the Institute of Cancer recommendations that reflex testing improves the speed of treatment decisions and improves patient care [12].

Strengths and limitations

The consensus recommendations were developed using robust methodology, following best-practice guidance for conducting Delphi research [13,37]. The two rounds of Delphi questionnaires were completed by independent, voluntary (non-reimbursed) participants. Although not all participants from the two rounds of Delphi validated the final recommendations; they were developed through discussion by both pathologists and oncologists during the consensus meeting, with consideration and incorporation of the comments provided from the Delphi participants. We should acknowledge that not all stakeholders were represented in the Delphi; for example, we did not recruit patients. Although a UK study, findings may be generalisable to a wider audience as many of the topics are valid at an international level.

Conclusions

This research has gathered and consolidated opinions from pathologists and oncologists working across the UK. The results support the need for standardisation and, importantly, demonstrate the challenges faced in clinical practice by those requesting and testing biomarkers for OGC, indicating significant concerns relating to pathologists and laboratory capacity. The recommendations reflect current best-practice and should be implemented to support rapid MDT decision-making within OGC.

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Author contribution

NW, WM, PT, and PC contributed to the study conception, including the development of questions and statements for the two rounds of Delphi. All authors attended the consensus meeting, contributed to the writing and review of the manuscript. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Data statement

BMS policy on data sharing may be found at the following site: https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

Informed consent

We completed the Health Research Authority (HRA) and UK Medical Research Council (MRC) decision tool to determine that this research did not require ethics committee approval (https://www.hra-decisiontools.org.uk/ethics/). The NHS HRA and UK MRC have the authority to waiver such studies from ethics committee approval; the NHS HRA and UK MRC deemed ethics approval was not necessary for our study according to their legislation [38,39]. All participants were made aware their participation was voluntary, were informed of the study purpose, risks and benefits and provided informed consent to participate. Participants were also made aware their responses were anonymous and they could withdraw at any time. We conducted the study according to the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines as appropriate.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Patrice Carter reports financial support was provided by Bristol Myers Squibb Co. N.P. West, W. Mansoor, P. Taniere, E. Smyth, M. Rodrigues-Justo, A. Oniscu reports a relationship with Bristol Myers Squibb Co that includes: consulting or advisory. PC is an employee of HEOR Ltd, which received funding from Bristol Myers Squibb for this study. NW declares consultancy fees from Bristol Myers Squibb, Astellas, GSK, Amgen and Pfizer. NW, WM, and PT declare consultancy fees from Bristol Myers Squibb for their time as part of the steering committee for this modified Delphi. All authors (except PC) were also paid consultancy fees for attending and contributing to the final consensus meeting by Bristol Myers Squibb. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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