BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-094343
Article Type:	Original research
Date Submitted by the Author:	28-Sep-2024
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Keywords:	Adult oncology < ONCOLOGY, Gastrointestinal tumours < ONCOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Results of a modified Delphi consensus on the optimal testing pathway for oesophago-gastric cancer care in the UK.

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ABSTRACT WORD COUNT: 249

MAIN ARTICLE WORD COUNT: 3586

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ABSTRACT

Objective

To develop expert consensus on the optimal testing pathway for OG cancer care.

Methods and analysis

The process followed a modified Delphi methodology to develop consensus on the optimal testing pathway for OG cancer care. In November 2023, a review of available literature on the topic of OG cancer was conducted. The results of this review informed a steering group discussion on the barriers and opportunities within the OG testing pathway. Six domains of focus were agreed and used to develop

36 agreed statements were developed into a Likert survey, which was distributed by a third party (M3 Global Research). Completed surveys were analysed to produce an arithmetic agreement score for each statement. The results were then reviewed by the steering group to agree any recommendations and conclusions.

Results

A total of 50 responses were received from consultant oncologists (n=25), pathologists (n=15), specialist oncology pharmacists (n=5), and specialist oncology nurses (n=5).

Consensus was achieved in 35/36 statements (97%). The steering group agreed a commentary on the results and a series of recommendations for best practice testing in OG cancer. Given the level of agreement and that the stopping criteria were met, it was decided not to undertake further Delphi rounds.

Conclusion

The recommendations support the use of a reflex testing approach for human epidermal growth factor receptor 2 (HER2), programmed death ligand 1 (PD-L1), and microsatellite instability high (MSI-H) / mismatch repair deficiency (dMMR) in patients diagnosed with OG cancer who are suitable for treatment with targeted therapy.

What is already known on this topic

Oesophago-gastric (OG) cancers are the fifth most common type of cancer in the UK, and patients with advanced disease have some of the worst outcomes among all cancers in England. With the move towards greater use of targeted treatments in OG cancer, there is a growing demand for histology/pathology services to support treatment decisions. This increase in demand requires careful planning to prevent unnecessary delays, which ultimately may prevent timely access to treatment and potentially lead to inferior outcomes for patients.

What this study adds

This study adds consensus from a multidisciplinary responder panel of experienced healthcare professionals regarding when reflex testing for biomarkers (HER-2, PD-L1, etc.) and a clear set of recommendations that can be implemented across OG cancer services that align with NHS priorities.

How this study might affect research, practice or policy

The outputs and recommendations should be used to promote local discussion of how OG testing can be adapted to reduce unnecessary delays and ultimately improve outcomes for patients. Whilst historically the use of a reflex testing approach may have been seen as problematic, in the context of the growing availability of targeted therapies for OG cancer, the NHS should consider how to enhance testing services to deliver optimal testing to support timely treatment decisions.

KEYWORDS

- Esophageal Neoplasms / diagnosis
- Stomach Neoplasms / diagnosis
- Adenocarcinoma / therapy
- Esophagogastric Junction / pathology
- Delphi Study

INTRODUCTION

Oesophago-gastric (OG) cancers, which affect the gullet and stomach, are the fifth most common type of cancer in the UK, with 13,000 people diagnosed annually in England and Wales.[1] Oesophageal cancers account for 72% of OG cancers, while stomach cancers make up the remaining 28%.[1] The most common types of OG cancer are adenocarcinoma and squamous cell carcinoma, with the former being the most prevalent in the UK.[2] One of the risk factors for OG cancer is the presence of Barrett's oesophagus, a metaplastic condition of the lower oesophagus associated with acid reflux.[3]

The treatment approach for OG cancer depends on several factors, including histological subtype, clinical stage, tumour location, presence of metastases, patient frailty/predicted treatment tolerance, and levels of treatment informing biomarkers such as human epidermal growth factor receptor 2 (HER2), programmed death ligand 1 (PD-L1), and the presence of microsatellite instability high (MSI-H)/mismatch repair deficiency (dMMR).[4] Treatment may involve a combination of surgery, chemotherapy, radiotherapy, and immunotherapy.[4]

There are a number of biomarker dependant targeted therapies now available, and more are in development.[5] These options play key role in treatment selection. For example, pembrolizumab and nivolumab are immune checkpoint inhibitors (ICIs) indicated for use in PD-L1 positive OG cancers but are used in different clinical situations depending on histological subtype, specific drug combination, and line of therapy.[5]

With the move towards greater use of targeted systemic treatments in OG cancer, there is a growing demand for histology/pathology services to support treatment decisions. This increase in demand requires careful planning to prevent unnecessary delays, which ultimately may prevent timely access to treatment if disease progression occurs as a consequence of delay.

In England, patients with OG cancer have some of the poorest outcomes among all cancers at present.[6] Between 2020 and 2022, 44% of patients had Stage 4 cancer at diagnosis, and in the year 2021/22, 69% of individuals referred via GP services waited longer than the target of 62 days from urgent referral to treatment initiation[7]. However, these patients are often symptomatic and require rapid access to treatment. The results of these delays could be that a patient is no longer fit to receive the optimal treatment, which could ultimately increase mortality. NHS England recognises that outcomes for OG cancer should be improved and has developed a best practice 28-day timed diagnostic pathway to support NHS providers in reducing waiting times and unwarranted variation in the diagnostic process.[6] This is a valuable start, but there is still a need to address biomarker testing to support how and when decisions are made to use targeted therapy (such as ICIs). In addition, MSI-H/dMMR status may influence treatment decisions, particularly in advanced and early-stage disease.[8]

Not every OG patient requires biomarker testing. Those receiving supportive care will not receive targeted treatment, and those in the early stages of disease may be under consideration for endoscopic or surgical therapies. However, patients suitable for targeted immunotherapy will ideally have reflex (i.e. testing at diagnosis of adenocarcinoma) biomarker testing for HER2, PD-L1, and MSI-H/dMMR at the earliest practical time. In practice, NICE recommendations require an established HER2- negative status to allow access for some immunotherapies.[9,10], leading to a prioritisation of HER2 testing over other possible biomarker testing.

Biomarker testing is associated with resource use and cost, and as demand for targeted treatment grows, so will the pressure on pathology services. To ensure that oncologists have all the information needed to select a targeted immunotherapy treatment at the appropriate time, local services should consider how best to develop local testing pathways (ideally in a scalable way) to ensure that oncologists are able to initiate the most appropriate treatment at the earliest opportunity.

The aim of this study was to develop expert consensus to inform an optimal testing pathway for OG cancer care.

MATERIALS AND METHODS

The process followed a modified Delphi methodology (Figure 1) guided by the ACcurate COnsensus Reporting Document (ACCORD) checklist 2024, to develop consensus on the optimal testing pathway for OG cancer care.

In November 2023, a review of available literature on the topic of OG cancer was conducted primarily on PubMed, Google Scholar, and clinical trial registration databases. Search terms included but were not limited to: 'oesophago-gastric cancer', 'immunotherapy, 'biomarkers', 'HER2', 'PD-L1', 'histology'. A general web search using free text terms based on the inclusion criteria was also conducted to locate any additional publications relevant to this topic.

Guided by an independent facilitator (Triducive Partners Limited), a steering group of healthcare practitioners (4 consultant oncologists and 2 consultant pathologists) experienced in the diagnosis and treatment of OG cancer was gathered. These individuals were selected based on published research and experience in the testing pathway/patient selection for targeted therapies. In addition, members of the group serve on the UK-National Cancer Research Institute clinical research groups, have acted as clinical experts for NICE and RCPath (Royal College Pathology) guidelines and are members of the ESMO (European Society of Medical Oncology) and International Academy of Pathology (IAP) faculty.

The information gathered from the literature review was used to develop key questions to drive the meeting discussion. During the meeting, the steering group agreed six broad domains to develop consensus statements around:

A. Patient profile and type

B. Testing pathway ideals

C. Standards/Benchmarks

D. Optimal roles and responsibilities to improve delivery of the testing pathway

E. NHS system readiness

F. Future considerations

Each domain was discussed in turn, and 39 statements were suggested by the steering group working collaboratively. The statements were then collated, and the steering group independently rated the statements as either “accept”, “remove”, “reword”, or suggested additional statements. During the review, recommendations were accepted based on a simple majority. This constituted the initial round of consensus.

The resulting statements were developed into a Likert survey, which was distributed by a third party (M3 Global Research) in Round 2 of the process.

Recruitment of panel members was according to the following criteria:

- Currently employed in the UK NHS
- Current role of either consultant oncologist, oncology specialist nurse, oncology specialist pharmacist, or pathologist
- Experienced, or currently involved in managing of OG cancers
- Pathologists must have responsibility for at least one of the following: diagnostic histopathology and/or molecular diagnostics

Anonymity of responders was planned into the study design, and no personal information beyond the current role and UK country was captured during the survey. The identity of respondents was not known to either the steering group or facilitator. M3 Global Research provided an incentive payment of up to £32 to panellists on the completion of the survey response.

Stopping criteria were established *a priori* as a maximum of 50 responses (comprising 25 consultant oncologists, 15 pathologists, 5 specialist oncology pharmacists, and 5 specialist oncology nurses), 90% of statements passing the threshold for consensus, and a threshold for consensus set at 75%, a widely accepted threshold.[11]

A statement of consent was included at the start of the survey, and consent was implied by the completion and submission of the survey. As this study only collected the anonymous opinions of healthcare professionals and no patient-specific data was captured, ethical approval was not sought.

Completed surveys were analysed to produce an arithmetic agreement score for each statement using Microsoft Excel software. The responses were aggregated to provide an overall agreement level (i.e., the number of respondents expressing agreement as a percentage of the overall number of responses for each statement). This information was then reviewed by the steering group to agree any recommendations and conclusions as a consequence.

Analysis of Round 2 was carried out in April 2024, and the second steering group meeting held two weeks later for analysis and discussion of results.

Patient and Public Involvement

None. The stated objective was to examine the opinions of experienced healthcare professionals towards the principles of an optimal testing approach for OG cancer care in the UK.

Data Availability Statement

Anonymised data is included in the supplemental materials (Figure S2).

RESULTS

During the first round of statement review with the members of the steering group, of the initial 39 statements, 3 were removed, and 5 were reworded, resulting in a final agreed set of 36 statements.

At the end of Round 2, completed questionnaires were received from a total of 50 respondents, all of which met the inclusion criteria (Table 1). Distribution of responses was as planned. The vast majority of respondents (n=47) were from England, with the remaining three from Scotland. No responses were received from Wales or Northern Ireland.

As the stopping criteria were satisfied, the steering group agreed that no further rounds were necessary.

Results from Round 2 showed very strong agreement (≥90%) in 22 (60%) statements, and strong agreement (<90% and ≥75%) in 13 (36%) of statements. The remaining one statement failed to achieve consensus (Table 1, Figure 2).

Distribution of consensus scores on the four-point Likert scale provided to respondents is represented in Figure S1.

The steering group reconvened to discuss further, agree the key points for development into a manuscript, and formulate a set of recommendations to support optimal testing in OG cancer. Both the manuscript content and recommendations were independently reviewed by the steering group prior to finalisation.

DISCUSSION

Overall, there was very strong agreement amongst responders to all proposed statements, with the exception of Statement 9 (70%). There appears to be good awareness and desire to deliver optimal care amongst responders. It is hoped that this data can provide evidence to support the implementation of optimised testing pathways for treatment decisions in OG cancer.

Responses were received from 50 healthcare professionals working across the OG care pathway, with representation from consultant oncologists, oncology specialist nurses, oncology specialist pharmacists, and pathologists. 47 of the 50 responses were from England, and no responses were received from Wales and Northern Ireland. It is, therefore, true to say that the responses largely reflect opinions from healthcare professionals in England. The conclusions and recommendations are therefore not necessarily directly applicable to practice in the other UK nations and may require local adaptation.

A. Patient profile and type

Respondents agreed (80%) that at the time of diagnosis, all patients should be tested to establish HER2, PD-L1, and MSI-H/dMMR status. This reflex testing approach (as opposed to sequential or on-demand) has the key benefit of ensuring results are available rapidly and in time for the first oncology consultation when the treatment plan is agreed. It also means that the patient may have to undergo fewer invasive biopsy procedures. There may be valid reasons why an individual should not be tested in this manner, such as those who are not suitable for systemic/targeted therapy. There are some key considerations for this approach that require careful planning: this approach relies on enough viable tissue being collected during biopsy, and testing all patients at diagnosis will place an increased demand on pathology services. The ideal approach is to test all patients who may receive systemic therapy for these three biomarkers at the time of diagnosis, and local services should consider what barriers exist to prevent this in practice and how these can be mitigated.

B. Testing pathway ideals

In the UK, variability exists in facilities and implementation of molecular testing services, which is dependent on local pathways and funding.[12] The Institute of Cancer Research (ICR) has stated that 'there needs to be a clearer route to the NHS for non-genomic biomarker tests, such as transcriptional, protein expression and immunohistochemistry tests' in recognition of the lack of a national system for non-genomic testing (as is in place for genomic tests).[13] This means that providers may struggle to provide reflex testing for non-genomic biomarkers at the point of diagnosis, which may delay

access to targeted treatments. Both American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) guidelines recommend first-line treatments according to biomarker status (e.g., HER2 and PDL-1) implying that molecular testing will have been completed prior to initiation.[4,14] This picture is reflective of the strong agreed that clear guidance is needed regarding when PD-L1 testing should be carried out (S3, 92%).

Pathology services to support PD-L1 testing may be either 'in-house' at the prescribing institution, or at a centralised testing hub that serves a local provider network. Both models have advantages and disadvantages. Centralised hubs offer efficiency and consistent quality control (S4, 94%), but there are logistic considerations regarding the transport of samples for testing and turnaround times to receive results back at the prescribing institution. In-house pathology services can, in theory, provide a quicker turnaround due to the fewer logistical requirements of sending samples off-site, but setting up and maintaining a laboratory facility requires significant investment and commitment. Regardless of the specific model in place, there should be a clear agreement to ensure that results are available prior to multidisciplinary team (MDT) discussion/treatment decision making to avoid delays in treatment initiation, which could result in worsening disease (S8, 96%). Although the majority of respondents agree that ideally, testing should be conducted in-house (S6, 70%), this statement did not achieve consensus agreement. On further analysis, there was a stark difference in response by role – pathologists' agreement was 47% compared with 80% agreement for all other roles, perhaps demonstrating appreciation amongst pathologists of the effort and complexity of setting up and maintaining in-house services.

There was strong agreement that reflex testing at the point of diagnosis offers benefits in reduced time to the initiation of treatment (S11, 82%), and is more cost-effective than sequential testing (S12, 80%). The responder panel very strongly supports reflex testing of all patients who are potentially suitable for systemic therapy (S13, 92%). Whilst no direct evidence exists regarding the cost-effectiveness of reflex testing in OG cancer, evidence does exist to support reflex testing approaches in other cancers. Gosney et al[15] investigated the cost-effectiveness of pathologist-initiated reflex testing in non-small-cell lung cancer (NSCLC). They concluded that timely biomarker testing is crucial for selecting first-line systemic therapy for patients, and reflex testing is expeditious and standardises the ordering of biomarker tests. The authors suggest that reflex testing must be governed by an MDT-defined protocol, and that this protocol requires collaboration between MDT and policymakers to ensure compliance with the latest guidelines and reimbursement criteria. A retrospective cohort study of newly diagnosed stage IV non-squamous NSCLC patients found that implementation of a reflex molecular testing pathway increased the proportion of patients who underwent comprehensive tissue-based molecular testing upon initial diagnosis.[16] Ideally, an audit or retrospective study addressing the cost-effectiveness/efficiency of using reflex vs sequential testing in OG cancer is needed to demonstrate logistical, time-to-treatment, or patient outcome gains in order to provide support for local business cases.

Intratumour, spatial (between baseline primary and metastatic tumours) and temporal (between tumour before and after chemotherapy) heterogeneity is well known in Upper GI cancers. Discrepancies rates have been reported in up to 33%

of cases between primary and metastatic deposit and concordance rates between tumours before and after chemotherapy varied between 57-63% of cases.[17,18] In addition in view of the risk of false negative scoring if only a single biopsy is taken, several groups have suggested that multiple biopsies (at least 6) are recommended for accurate diagnosis, biomarkers and molecular analysis of upper GI cancer.[4] Although it has been suggested that multiple biopsies of primary and metastatic sites might need to be tested before considering treatment options, there are no consensus guidelines to recommend testing of metastatic deposit of re-biopsy after neo-adjuvant therapy if the diagnostic biopsy was PD-L1 negative.

C. Standards/Benchmarks

Here, 94% of respondents agreed that biomarker tests should be turned around within 10 working days (S14), but a lower agreement was achieved regarding the return of results within 5 working days from receipt of the sample by the pathology lab (S15, 78%). Pathologists exhibited only 47% agreement with S15, perhaps as they are aware of the logistical challenges in delivering results within 5 days. There is a need for clear UK standard guidelines regarding how a realistic turnaround time (perhaps 10 days in line with S14) can be achieved agnostic of laboratory setting. These guidelines should also stipulate that the laboratory facility must be the International Standards Organisation (ISO) 15189 United Kingdom Accreditation Service (UKAS) approved (S16, 94%).

Respondents agree that from request to results, the testing process is often delayed by logistical issues (S17, 76%). The response by role is interesting as oncologists were the only role group with a response above the consensus threshold (84%), suggesting that if responder numbers were equal amongst these groups, then this statement would not have achieved consensus.

The key aim for optimising the testing pathway is to ensure that all relevant information is available to the MDT/oncologist to allow for the most appropriate treatment to be recommended from the outset. This currently includes HER2, PD-L1, and MSI-H/dMMR status but is likely to expand as new targeted/biomarker driven therapies become available in the future. This should be accepted as the 'gold standard' for OG cancer care. The NHS England best practice timed pathway[6] proposes a 28-day period from referral through diagnosis to the first outpatient clinic; biopsy to support diagnosis is scheduled within 7 days, once the diagnosis is confirmed (by Day 14) there is a 14-day window for biomarker status testing provided appropriate samples can be collected at biopsy.

D. Optimal roles and responsibilities to improve delivery of the testing pathway

There was very strong agreement that a lack of coordination between disciplines can impact the testing pathway (S24, 96%), and that a dedicated coordinator should be in place to manage the test process from request to results dissemination (S25, 84%). The role of the MDT is pivotal in ensuring that treatment is planned appropriately, and the

National Institute for Health and Care Excellence (NICE) Oesophago-gastric cancer Quality Standards define the core roles of the full MDT, but this can be augmented as needed.[19]

If results of biomarker testing are to be available for the 1st outpatient appointment with the oncologist, an efficient process must be implemented to minimise any potential logistical delays. The MDT should agree, document, and implement and audit appropriate performance measure (key performance indicators/KPIs) for the OG testing pathway to identify where delays occur and to modify the pathway to release these bottlenecks. Performance data can also be used to support business cases for improvements to the pathway and quantify the impact of making improvements versus the current status quo.

E. NHS system readiness

Results from this section demonstrate that there is strong agreement that the NHS and industry should work more collaboratively in horizon scanning of future technologies. This would provide a greater opportunity for the NHS to put services in place to support new technologies and also agree requirements to manage capacity according to anticipated demand for specific technologies (e.g., use of Dako versus Ventana technologies for biomarker testing). There is also potential for NHS pathology services to explore how the use of artificial intelligence (AI) might improve diagnostic efficiency – as is being realised in other therapy areas.[20,21]

As part of 'future readiness', educational programmes should be in place for all MDT roles at the earliest practical point to support clinical decisions (S31, 96%).

It is also important that the NHS and NICE agree that when a technology is undergoing appraisal for cost-effectiveness, the costs of processes that are essential for meeting the reimbursement criteria (as set out by NICE) are packaged as part of the reimbursement package (S34, 98%). This is to avoid the situation where the availability of funding for diagnostic tests may act as a potential barrier to expediting recommended treatment initiation.

Strengths and limitations

All statements (with one exception) achieved consensus agreement, suggesting either that the responders recognise and agree with the perspectives of the steering group, or that the statements were (unconsciously) designed to be agreeable – indicating potential bias. Given the observed variation in responses to some statements, it is possible that had the roles been represented equally, the proportion of statements achieving consensus may have been different. In addition, a larger total cohort of responders would have provided greater certainty that the opinions expressed were representative of each individual role.

The responses from outside of England were low, with only 3 responses from Scotland and none from Wales or Northern Ireland, potentially reducing the applicability of the recommendations made here to these health systems. There is a clear need to understand the opinions of healthcare professionals in the devolved nations to provide a comparison and extend the remit of this work and further work should be focused on this. As a consequence, where policy and reimbursement have been discussed, the focus had been kept on the NHS in England to represent the responder demographic.

The patient experience has not been investigated (as it was outside of the scope of the study objectives), but it would be valuable in providing feedback on how problems in the current testing pathway can impact the individual, and, also, what steps in the process that patients consider a priority.

RECOMMENDATIONS

Based on the survey results and subsequent discussions within the steering group, the authors propose the following recommendations to support treatment decisions in OG cancer. A proposed diagnostic pathway that reflects the recommendations is included in Figure 3.

1. All patients suitable for systemic therapy should be tested for HER2, PD-L1, and MSI-H/dMMR at the time of diagnosis
2. A dedicated coordinator should be in place to plan, request, and coordinate dissemination of test results
3. Results of biomarker testing should be available within 10 days of request
4. All tests should be conducted by an approved United Kingdom Accreditation Service (UKAS) laboratory
5. Automatic transfer of specific tissue cores should be in place for centralised processing
6. All test results should be made available on a single, integrated report
7. All test results should be with the MDT/oncologist prior to the first consultation post-diagnosis
8. Treatment should be initiated within 30 days of receiving biomarker test results at the latest
9. All testing pathways should have MDT agreed KPIs in place and tracked for audit purposes
10. Funding and reimbursement routes for mandatory diagnostic tests should be bundled with any NICE-approved treatments

To facilitate implementation of these recommendations, local services may need to construct a business case to ensure funding is in place for reflex testing (and associated pathology resource requirements). Providers should also engage

with NHS, ICR and NICE regarding the potential for national provision of molecular testing as is currently in place for genomic testing.

CONCLUSION

This modified Delphi exercise was able to achieve agreement from a panel of 50 experts currently involved in OG cancer for 35 of 36 statements. In this paper we have described the current heterogeneity that exists in the UK NHS regarding the provision of molecular pathology in OG cancer, the results demonstrate clear recognition amongst responders of the need for clarity and standardisation of the testing pathway for OG cancer. These recommendations are designed to set a minimum bar for OG cancer services to ensure greater concordance between providers in patient experience and access to licensed and guideline-recommended treatments.

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SUPPLEMENTAL INFORMATION

Supplemental Figure (S1)

Anonymised Results Data

DECLARATIONS

This study did not require registration because neither the assigned interventions nor the outcomes assessed were related to the health of participants.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

FUNDING

MSD pharmaceuticals initiated and supported this consensus project including the selection of faculty of experts. MSD paid the expert group honorarium. MSD commissioned Triducive Ltd (UK) to facilitate the project and analyse the responses to the consensus statements, in line with Delphi methodology. MSD had no input into drafting or publication of the manuscript.

CONFLICTS OF INTEREST

All authors received honoraria from MSD while undertaking this study. MSD commissioned Triducive Partners Limited to facilitate the project and analyse the responses to the consensus statements in line with the Delphi methodology.

Author declarations:

The authors state the following conflicts of interest:

MR-J has received honoraria for attendance at advisory boards, chairing educational meetings, consultancy, travel, accommodation and registration at national/international meetings from BMS, MSD, Roche Diagnostics Solutions, Agilent, Ibex Medical and research/educational grants from Pfizer and Roche Diagnostics Limited.

TB has received lecture fees from MSD, AstraZeneca and Elekta, and consulting fees from MSD.

ME has received sponsorship from MSD to attend an international conference and honoraria from MSD and BMS and Servier for advisory work.

The following authors state no conflicts of interest: WM, NS, PT.

AUTHORS' CONTRIBUTIONS

All views expressed by the authors are those of the individual and do not represent those of their organisation/place of work. Contributors MRJ, WM, TB, ME, NS, PT agreed the design of the study, formulated and reviewed the statement set. Results of the study were discussed by all contributors as part of a formal Steering Group meeting where commentary was agreed for development into the initial draft manuscript. MRJ, WM, TB, ME, NS, PT took an equal role in reviewing the initial manuscript draft and providing comments, and all approved the final draft. MRJ is the guarantor for the work and/or conduct of the study, had access to the data and controlled the decision to publish.

ACKNOWLEDGEMENTS

The authors wish to thank Tim Warren and Ian Walker from Triducive Partners Limited for their support in collating the data, analysing the results, drafting the initial manuscript, and reviewing the final draft. This project was initiated & funded by MSD UK Ltd.

TABLES AND FIGURE LEGENDS

Table 1. Defined consensus statements and corresponding levels of agreement

No:	Statement:	Strongly Agree	Tend To Agree	Tend To Disagree	Strongly Disagree	Overall Agreement
Domain A: Patient profile and type						
1	All patients should be tested for HER2, PD-L1 and MSI-H/dMMR at time of diagnosis	46%	34%	6%	14%	**80%**
2	All patients considered potentially suitable for systemic therapy should be tested for HER2, PD-L1 and MSI-H/dMMR	64%	26%	0%	10%	**90%**
Domain B: Testing pathway ideals						
3	There is a need for clear guidance on which stage of the pathway PD-L1 testing should be used	44%	48%	2%	6%	**92%**
4	A centralised, testing service can provide more efficiency and quality control in the service	42%	52%	2%	4%	**94%**
5	PD-L1 testing should be completed in advance of MDTs to inform decision making	42%	44%	10%	4%	**86%**
6	Ideally, testing should be conducted within the prescribing institution	24%	46%	26%	4%	**70%**
7	Variance in the testing pathway leads to delays in patients accessing appropriate treatment	32%	58%	8%	2%	**90%**
8	A delay in the diagnostic process may potentially prevent optimal treatment entirely if the patient's disease worsens significantly	48%	48%	2%	2%	**96%**
9	It would be beneficial for automatic transfer of specific tissue cores to be in place for centralised processing	38%	50%	10%	2%	**88%**
10	Treating physicians need to be informed promptly when there is insufficient tissue to satisfy testing requirements and so re-biopsy may be indicated	66%	30%	2%	2%	**96%**
11	Reflex testing at the point of diagnosis is more efficient than sequential testing and may reduce the time to initiation of treatment	38%	44%	16%	2%	**82%**
12	Reflex testing at the point of diagnosis is more cost-effective than sequential testing	30%	50%	16%	4%	**80%**
13	Reflex testing at the point of diagnosis is recommended in all patients considered potentially suitable for systemic therapy	46%	46%	2%	6%	**92%**
Domain C: Standards/Benchmarks (inc. reference centre v in-house testing v regional hubs)						
14	Biomarker tests should be turned around within 10 working days	42%	52%	2%	4%	**94%**
15	Results of biomarker tests should be available no longer than 5 working days from the day the sample arrives at the pathology laboratory	30%	48%	12%	10%	**78%**
16	Either in-house or outsourced, tests need to be delivered by an approved United Kingdom Accreditation Service (UKAS) laboratory	52%	42%	4%	2%	**94%**
17	The process from requesting a test to receiving the results is often unduly delayed by logistical issues	32%	44%	20%	4%	**76%**
18	All test results should be made available on a single, integrated report	50%	40%	8%	2%	**90%**
19	All test results should be with the oncologist prior to the first consultation post-diagnosis	48%	38%	10%	4%	**86%**
20	If there is insufficient tissue for biomarker testing, this should be discussed at the MDT	48%	48%	2%	2%	**96%**
21	Treatment should be initiated within 30 days of receiving biomarker test results	46%	44%	8%	2%	**90%**
22	Positivity rates should be audited for the specific PD-L1 assay for comparison with literature-reported rates	42%	52%	4%	2%	**94%**
Domain D: Optimal roles and responsibilities to improve delivery of the testing pathway						

23	Clearly defined roles and responsibilities for each stage in the testing pathway would benefit the efficiency	44%	52%	2%	2%	**96%**
24	Lack of co-ordination between disciplines involved in the testing pathway can limit efficiency of the process	38%	56%	4%	2%	**94%**
25	A dedicated coordinator should be in place to plan, request, and coordinate dissemination of the results of tests	40%	44%	14%	2%	**84%**
26	The MDT is responsible for ensuring that the correct testing pathway is in place	48%	38%	10%	4%	**86%**
27	The testing pathway should have agreed and documented time and KPI targets	36%	52%	8%	4%	**88%**
28	Testing pathway performance should be measured by the MDT	34%	44%	18%	4%	**78%**
29	Business cases can benefit the establishment of consistent testing pathways that are efficient and accessible	38%	56%	4%	2%	**94%**
Domain E: NHS system readiness						
30	Collaborative horizon scanning between NHS and industry would be beneficial to help NHS readiness (scan and test machines, learn from HER2	30%	68%	0%	2%	**98%**
31	Education of the entire MDT is vital to improve NHS system readiness for new tests and treatment modalities	54%	42%	2%	2%	**96%**
32	Any advent of technology and testing use needs to consider capacity concerns in the NHS	50%	46%	2%	2%	**96%**
33	Any advent of technology and testing use needs to consider resource requirements rather than just acquisition costs	46%	34%	6%	14%	**94%**
34	NHS and NICE need to work more collaboratively so when new therapies are approved there is resource in the NHS provision for the accompanying biomarker test	64%	26%	0%	10%	**98%**
Domain F: Future considerations						
35	A coordinated industry group to liaise with NHS and policy makers could help support future utilisation of new tests and modalities	44%	48%	2%	6%	**92%**
36	Artificial Intelligence technologies have the potential to improve the speed with which test results are analysed and processed	42%	52%	2%	4%	**88%**

Figure 1. Modified Delphi study design

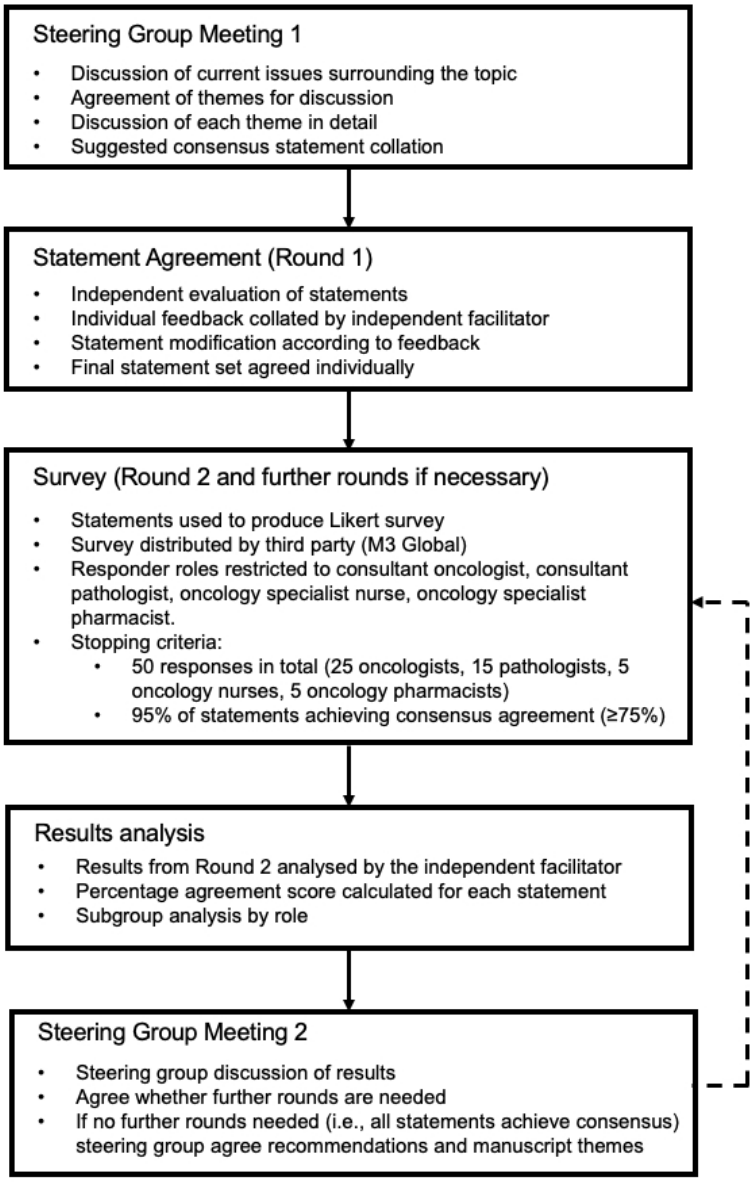
Figure 2. Consensus agreement levels by statement. The threshold for consensus is depicted by the green line (75%). The blue line signifies the threshold for very strong agreement (90%)

Figure 3. Potential diagnostic pathway and indicative timescales. Based on consensus results and NHS England 28-day best practice timed pathway[6]

Supplemental figures

Figure S1. Percentages of agreement level by statement

Figure S2. Consensus Survey Results Data



Modified Delphi study design

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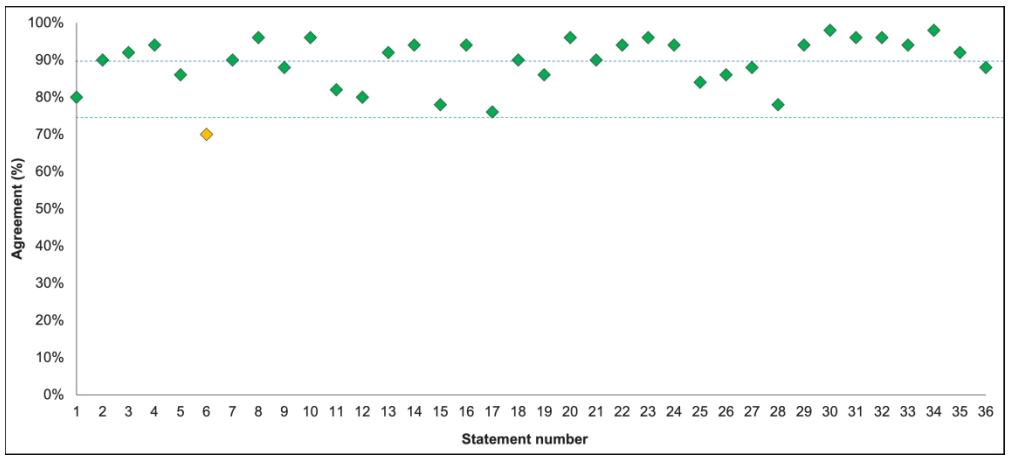

Consensus agreement levels by statement. The threshold for consensus is depicted by the green line (75%). The blue line signifies the threshold for very strong agreement (90%)

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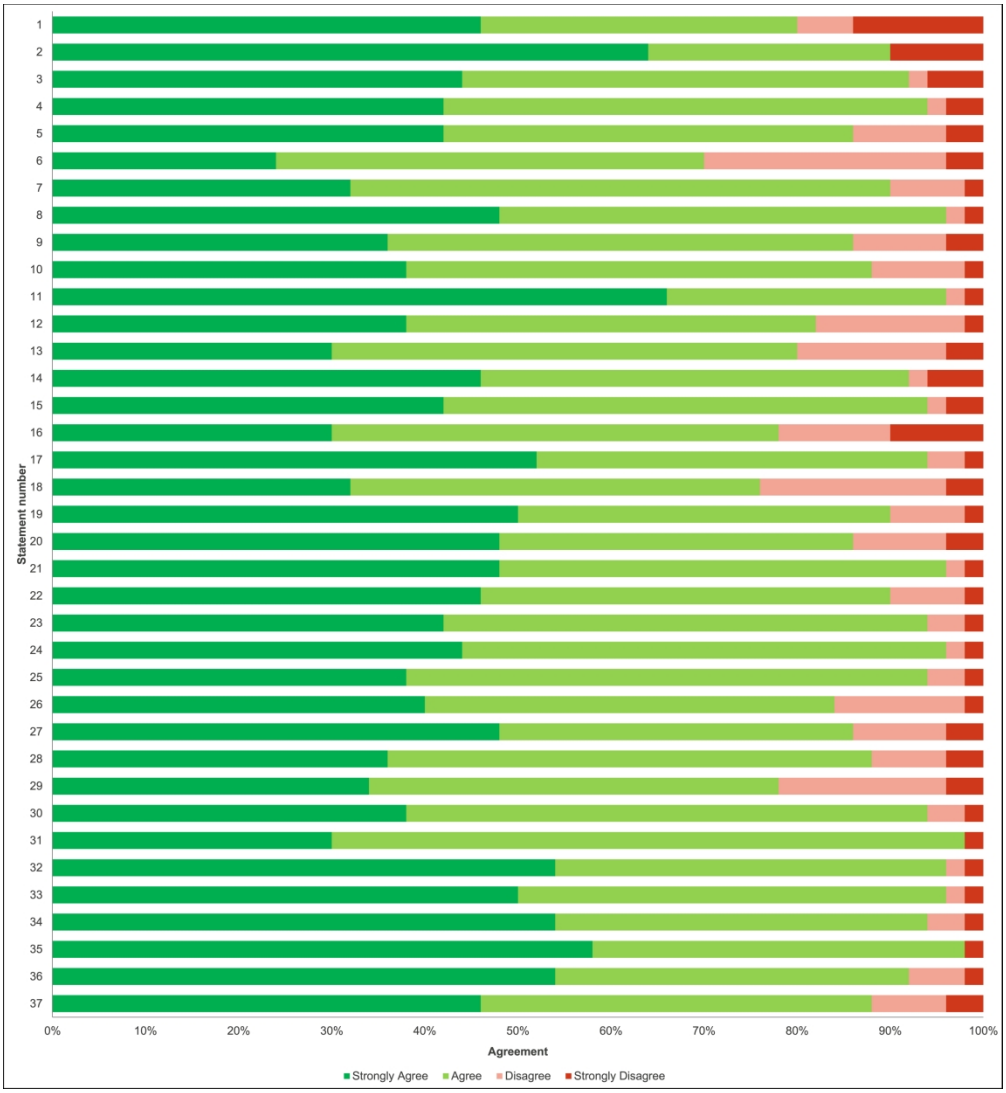
Diagnosis			MDT	1st Outpatient Clinic
Day 0	Day +3	Day +4	Day +10	Day +18
Oesophago-gastro-duodenoscopy (OGD) to BSG/AUGIS quality standards Trans-nasal endoscopy (TNE) Whole-body CT scan Biopsy samples taken to support molecular testing	Diagnostic histology results reported	F-18 FDG PET-CT (within 24 hours) for those suitable for radical treatment (except for T1a tumours) +/- endoscopic ultrasound +/- staging laparoscopy Reflex biomarker tests requested for HER2, PD-L1, MSI-H/dMMR for those who may receive a targeted therapy	Specialist MDT Results of biomarker testing reported in 1 standardised report	Outpatient clinic Assessment of fitness to treat Agree personalised treatment plan Patient optimisation

Potential diagnostic pathway and indicative timescales. Based on consensus results and NHS England 28-day best practice timed pathway6

711x407mm (72 x 72 DPI)

		ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50
		Specialty (1=Consultant Oncologist, 2=Consultant Pathologist, 3=Specialist Oncology Nurse, 4=Specialist Oncology Pharmacist)	4	4	3	1	1	1	1	1	3	3	1	1	1	4	1	1	4	4	3	1	1	2	1	1	1	1	1	1	2	2	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2
	Pathologist specific focus	Histopathology																						1							1	1								1	1	1	1	1	1	1	1	1	1	1	1	1	1
		Molecular Diagnostics																						0							0	0								0	0	0	0	1	0	0	0	0	1	1	1
		Coagulation																						0							0	0								0	0	0	0	0	0	0	0	0	0	0	0	0
		Haematology																						0							0	0								0	0	0	0	0	0	0	0	0	0	0	0	0
		Immunology																						0							0	0								0	0	0	0	0	0	0	0	0	0	0	0	0
		Toxicology																						0							0	0								0	0	0	0	0	0	0	0	0	0	0	0	0
		None of the above																						0							0	0								0	0	0	0	0	0	0	0	0	0	0	0	0
		Are you currently involved with, or do you have experience with, oesophago-gastric canc	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Do you have experience testing for PDL1 in oesophago-gastric cancers?																						Y							Y	Y								Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Where is your primary place of work? (1=England, 2=Scotland, 3=Northern Ireland, 4=Wales)	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1
		What is the estimated number of cases of oesphago-gastric cancer do you see each year? (1=<20, 2=20-50, 3=>50)	3	3	3	2	1	1	2	3	3	3	2	3	2	3	2	2	2	1	3	3	3	3	3	2	2	2	2	3	3	2	2	2	2	3	3	3	3	3	2	2	2	3	1	2	1	1	2	3	2	2
Statement number (1=Strongly Disagree, 2=Disagree, 3=Agree, 4=Strongly Agree)	1	All patients should be tested for HER2, PD-L1 and MSI/DMMR at time of diagnosis	3	4	4	4	4	1	3	4	1	4	3	4	3	4	3	2	3	1	3	3	4	4	4	1	3	4	3	4	4	4	1	2	4	4	4	3	4	4	4	3	4	1	3	4	3	3	1	4	2	4
	2	All patients considered potentially suitable for systemic therapy should be tested for HER	4	4	4	4	4	1	4	4	1	4	3	4	4	4	4	4	4	3	1	3	3	4	4	4	4	3	4	3	4	4	4	4	4	4	3	4	4	4	4	3	4	1	3	4	3	3	1	4	4	4
	3	There is a need for clear guidance on which stage of the pathway PD-L1 testing should b	3	3	4	3	4	3	3	4	1	4	4	3	4	4	4	4	4	4	1	3	3	3	2	3	3	1	3	3	4	3	4	4	4	3	4	4	4	4	3	4	3	4	3	4	3	4	3	4	3	3
	4	A centralised, testing service can provide more efficiency and quality control in the servic	3	4	4	4	3	4	3	3	1	4	3	4	3	4	4	3	3	3	4	3	4	4	1	3	4	3	3	4	3	3	3	4	3	3	4	3	3	3	3	4	3	3	3	2	4	3	4	4	4	4
	5	PD-L1 testing should be completed in advance of MDTs to inform decision making	2	4	4	4	3	4	4	3	1	4	4	3	4	4	4	3	3	3	3	4	3	4	4	4	2	4	3	2	4	1	3	4	4	4	4	3	3	4	3	3	3	2	3	4	2	3	3	3	3	3
	6	Ideally, testing should be conducted within the prescribing institution	4	4	4	4	2	3	4	4	3	1	4	3	3	3	2	3	3	3	3	4	3	3	2	4	3	4	3	3	4	1	2	4	4	3	4	2	2	4	3	2	3	2	3	3	2	3	3	2	2	3
	7	Variance in the testing pathway leads to delays in patients accessing appropriate treatm	3	4	4	3	3	4	3	4	1	4	3	4	3	3	2	3	3	2	3	3	3	3	4	3	4	3	4	3	3	4	3	4	4	3	4	4	4	4	4	3	4	4	3	3	3	3	3	4	2	3
	8	A delay in the diagnostic process may potentially prevent optimal treatment entirely if the	4	4	4	4	4	4	3	3	1	4	2	3	3	4	3	4	3	3	3	3	3	4	3	4	3	4	3	3	4	3	3	4	4	4	4	4	4	4	4	4	3	3	4	3	3	3	3	3	4	3
	9	It would be beneficial for automatic transfer of specific tissue cores to be in place for cen	3	3	4	4	4	4	3	3	1	4	4	3	4	3	4	3	4	3	3	3	3	3	4	4	3	4	4	3	3	4	2	3	4	4	4	4	4	4	3	4	2	2	3	2	3	3	3	2	4	3
	10	Treating physicians need to be informed promptly when there is insufficient tissue to sati	4	4	4	4	4	4	4	4	1	4	3	3	4	4	4	4	4	4	3	3	4	4	4	2	4	3	3	4	4	4	4	4	4	3	4	3	3	4	4	3	4	4	3	4	4	3	4	3	4	4
	11	Reflex testing at the point of diagnosis is more efficient than sequential testing and may	3	3	4	4	4	3	3	4	1	4	3	4	2	3	4	3	3	3	3	3	2	4	4	4	3	3	3	4	2	4	4	4	4	3	4	2	2	4	3	3	4	4	2	4	3	3	4	2	4	3
	12	Reflex testing at the point of diagnosis is more cost-effective than sequential testing	2	2	4	4	4	4	3	4	1	4	3	4	2	3	3	3	3	3	3	3	3	4	4	2	3	3	2	4	1	3	4	4	4	2	4	3	3	4	2	4	3	3	3	4	2	3	4	3	3	3
	13	Reflex testing at the point of diagnosis is recommended in all patients considered poten	3	3	4	4	4	4	3	4	1	3	4	4	1	3	3	3	3	3	3	3	4	4	4	3	3	3	3	4	1	4	4	4	4	4	4	4	4	4	3	3	4	4	2	4	3	3	4	4	4	3
	14	Biomarker tests should be turned around within 10 working days	3	3	3	3	3	4	3	4	1	3	3	3	4	4	4	3	2	4	3	3	4	3	4	3	3	3	4	4	3	3	4	4	4	4	4	4	4	4	4	4	3	1	3	4	3	3	4	3	4	4
	15	Results of biomarker tests should be available no longer than 5 working days from the d	3	4	4	4	3	3	4	4	1	4	3	3	3	3	4	3	3	1	3	3	3	2	4	2	3	3	3	4	1	2	3	4	4	3	4	3	3	4	3	4	2	2	1	3	2	3	3	1	4	4
	16	Either in-house or outsourced, tests need to be delivered by an approved United Kingdo	3	4	4	4	3	3	3	4	1	4	4	3	4	4	4	3	3	3	4	3	4	4	4	3	3	3	3	3	4	4	4	4	4	4	4	3	3	3	4	4	3	4	4	4	4	3	4	4	4	3
	17	The process from requesting a test to receiving the results is often unduly delayed by log	2	3	3	3	3	2	3	4	1	4	4	4	3	4	2	3	2	3	2	3	4	1	4	2	2	3	3	4	2	3	4	4	4	4	4	4	4	4	3	4	4	3	3	3	2	3	3	2	4	3
	18	All test results should be made available on a single, integrated report	3	4	4	4	2	4	3	4	1	4	3	3	4	4	4	3	3	3	3	3	4	3	4	4	4	3	3	4	3	4	4	4	4	2	4	3	2	4	4	4	4	2	3	4	3	3	4	3	4	4
	19	All test results should be with the oncologist prior to the first consultation post-diagnosis	3	4	3	4	3	4	3	4	1	4	4	2	3	3	4	3	2	4	3	3	4	4	4	2	4	3	3	4	2	4	3	4	4	3	4	4	4	4	3	3	4	1	3	4	2	3	4	4	3	3
	20	If there is insufficient tissue for biomarker testing, this should be discussed at the MDT	4	4	4	4	3	4	4	4	3	1	4	3	3	3	3	3	4	3	3	3	3	4	4	4	3	2	3	4	4	4	3	3	3	4	4	4	4	4	3	4	4	4	3	4	3	4	3	3	3	3
	21	Treatment should be initiated within 30 days of receiving biomarker test results	4	4	4	4	4	4	3	3	1	4	2	4	4	4	4	3	3	4	3	3	3	2	4	4	4	3	3	4	3	3	4	4	3	4	4	3	3	4	2	4	3	3	4	2	3	4	4	3	4	3
	22	Positivity rates should be audited for the specific PD-L1 assay for comparison with literat	3	4	4	4	3	3	3	4	1	4	4	3	2	3	4	3	3	3	3	3	3	3	4	3	4	3	3	4	3	3	2	2	2	3	4	4	3	3	3	4	4	3	4	4	3	3	4	4	4	4
	23	Clearly defined roles and responsibilities for each stage in the testing pathway would be	4	4	4	4	4	3	3	3	1	4	3	4	4	4	4	3	3	4	3	3	3	3	4	3	4	3	3	3	4	3	3	4	4	3	4	4	4	4	3	3	4	4	3	4	4	3	3	3	4	3
	24	Lack of co-ordination between disciplines involved in the testing pathway can limit efficie	3	4	4	4	3	3	3	3	1	4	3	4	4	4	3	3	4	4	3	3	3	3	4	3	3	3	3	4	3	3	4	4	4	3	4	4	3	3	3	3	4	4	3	3	4	4	3	3	3	4
	25	A dedicated coordinator should be in place to plan, request, and coordinate disseminati	2	3	4	3	3	4	3	4	1	4	4	4	4	3	4	3	3	3	4	3	3	3	4	2	3	3	3	4	2	2	3	4	4	4	4	2	4	4	3	3	4	2	3	4	3	3	3	3	4	2
	26	The MDT is responsible for ensuring that the correct testing pathway is in place	2	4	3	4	3	4	3	4	1	4	4	1	4	3	2	3	3	4	4	3	4	4	2	3	3	3	3	4	4	3	4	4	3	4	4	4	4	4	3	4	4	2	3	4	3	3	4	2	3	3
	27	The testing pathway should have agreed and documented time and KPI targets	3	4	3	4	4	3	4	4	1	4	3	2	4	3	4	3	3	3	4	3	4	3	4	2	4	3	3	4	2	3	4	4	1	3	4	3	3	3	3	3	3	1	3	4	3	3	3	3	3	3
	28	Testing pathway performance should be measured by the MDT	2	2	3	4	3	4	4	4	1	4	4	3	4	3	4	3	3	3	3	2	3	4	2	4	2	2	2	3	3	4	2	3	3	4	4	4	4	3	3	3	4	1	3	4	2	3	3	3	3	2
	29	Business cases can benefit the establishment of consistent testing pathways that are effi	3	4	4	3	4	2	3	3	1	4	4	3	4	4	3	3	3	4	4	3	4	3	4	3	3	3	3	3	4	3	3	3	4	3	3	4	4	3	3	4	3	3	4	3	3	4	3	3	4	3
	30	Collaborative horizon scanning between NHS and industry would be beneficial to help f	3	4	4	3	3	4	3	3	1	3	3	4	3	4	3	3	3	3	4	3	3	3	4	3	3	3	3	3	3	3	3	3	3	3	4	4	4	3	3	3	3	3	3	4	4	4	3	3	4	3
	31	Education of the entire MDT is vital to improve NHS system readiness for new tests and	3	4	4	4	4	4	4	3	1	4	4	3	3	4	4	3	3	3	4	4	3	4	4	4	4	4	3	3	3	3	3	2	3	4	3	4	3	3	3	4	4	4	3	4	3	3	4	4	4	3
	32	Any advent of technology and testing use needs to consider capacity concerns in the NH	3	4	3	4	3	3	4	4	1	4	3	3	3	4	4	3	3	3	4	4	3	4	4	4	4	4	3	3	3	3	4	4	4	3	4	4	3	3	3	3	3	3	3	4	4	3	4	2	3	3
	33	Any advent of technology and testing use needs to consider resource requirements rath	3	4	4	3	3	3	4	4	1	3	3	2	4	4	4	3	3	4	3	3	3	3	4	4	3	4	3	3	4	4	4	4	4	3	2	4	4	4	3	3	4	4	4	3	3	4	4	3	4	4
	34	NHS and NICE need to work more collaboratively so when new therapies are approved	3	4	4	4	4	4	3	4	1	4	4	3	4	4	4	3	3	3	4	4	3	3	4	3	4	3	3	4	4	4	4	4	4	3	4	4	3	3	4	4	4	4	3	4	4	4	3	3	4	4
	35	A coordinated industry group to liaise with NHS and policy makers could help support fu	2	4	4	4	4	3	3	4	1	4	3	4	4	4	4	3	3	4	4	3	4	2	4	3	4	3	3	4	2	3	4	4	4	3	4	4	4	4	3	4	3	3	4	4	3	3	3	4	4	3
	36	Artificial Intelligence technologies have the potential to improve the speed with which te	3	4	4	3	3	2	4	3	1	4	4	3	4	3	2	3	4	4	3	3	4	3	1	3	4	3	3	4	2	2	4	4	4	4	4	3	3	4	4	3	4	4	3	4	3	4	3	3	4	4



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BMJ Open

Results of a modified Delphi consensus on the optimal testing pathway for oesophago-gastric cancer care in the UK.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-094343.R1
Article Type:	Original research
Date Submitted by the Author:	03-Jan-2025
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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Adult oncology < ONCOLOGY, Gastrointestinal tumours < ONCOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Gastrointestinal tumours < GASTROENTEROLOGY

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Results of a modified Delphi consensus on the optimal testing pathway for oesophago-gastric cancer care in the UK.

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ABSTRACT WORD COUNT: 249

MAIN ARTICLE WORD COUNT: 3586

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ABSTRACT

Objective

To develop expert consensus on the optimal testing pathway for OG cancer care.

Methods and analysis

The process followed a modified Delphi methodology to develop consensus on the optimal testing pathway for OG cancer care. In November 2023, a review of available literature on the topic of OG cancer was conducted. The results of this review informed a steering group discussion on the barriers and opportunities within the OG testing pathway. Six domains of focus were agreed and used to develop

36 agreed statements were developed into a Likert survey, which was distributed by a third party (M3 Global Research). Completed surveys were analysed to produce an arithmetic agreement score for each statement. The results were then reviewed by the steering group to agree any recommendations and conclusions.

Results

A total of 50 responses were received from consultant oncologists (n=25), pathologists (n=15), specialist oncology pharmacists (n=5), and specialist oncology nurses (n=5).

Consensus was achieved in 35/36 statements (97%). The steering group agreed a commentary on the results and a series of recommendations for best practice testing in OG cancer. Given the level of agreement and that the stopping criteria were met, it was decided not to undertake further Delphi rounds.

Conclusion

The recommendations support the use of a reflex testing approach for human epidermal growth factor receptor 2 (HER2), programmed death ligand 1 (PD-L1), and microsatellite instability high (MSI-H) / mismatch repair deficiency (dMMR) in patients diagnosed with OG cancer who are suitable for treatment with targeted therapy.

Strengths and limitations of this study

- Agreement was achieved for all but one of the statements based on 50 responses from a multi-disciplinary panel
- The methodology developed consensus statements with an expert steering group for testing with an anonymous panel, minimising the potential for social bias
- The majority of responses were from England, therefore the developed recommendations may not directly apply to services in Scotland, Wales and Northern Ireland.

- The two key responder roles (oncologists and pathologists) were not equally represented in the Delphi panel, therefore the overall results may be biased in favour of oncologists.

KEYWORDS

- Esophageal Neoplasms / diagnosis
- Stomach Neoplasms / diagnosis
- Adenocarcinoma / therapy
- Esophagogastric Junction / pathology
- Delphi Study

INTRODUCTION

Oesophago-gastric (OG) cancers, which affect the gullet and stomach, are the fifth most common type of cancer in the UK, with 13,000 people diagnosed annually in England and Wales.[1] Oesophageal cancers account for 72% of OG cancers, while stomach cancers make up the remaining 28%.[1] The most common types of OG cancer are adenocarcinoma and squamous cell carcinoma, with the former being the most prevalent in the UK.[2] One of the risk factors for OG cancer is the presence of Barrett's oesophagus, a metaplastic condition of the lower oesophagus associated with acid reflux.[3]

The treatment approach for OG cancer depends on several factors, including histological subtype, clinical stage, tumour location, presence of metastases, patient frailty/predicted treatment tolerance, and levels of treatment informing biomarkers such as human epidermal growth factor receptor 2 (HER2), programmed death ligand 1 (PD-L1), and the presence of microsatellite instability high (MSI-H)/mismatch repair deficiency (dMMR).[4] Treatment may involve a combination of surgery, chemotherapy, radiotherapy, and immunotherapy.[4]

There are a number of biomarker dependant targeted therapies now available, and more are in development.[5] These options play key role in treatment selection. For example, pembrolizumab and nivolumab are immune checkpoint inhibitors (ICIs) indicated for use in PD-L1 positive OG cancers but are used in different clinical situations depending on histological subtype, specific drug combination, and line of therapy.[5]

With the move towards greater use of targeted systemic treatments in OG cancer, there is a growing demand for histology/pathology services to support treatment decisions. This increase in demand requires careful planning to prevent unnecessary delays, which ultimately may prevent timely access to treatment if disease progression occurs as a consequence of delay.

In England, patients with OG cancer have some of the poorest outcomes among all cancers at present.[6] Between 2020 and 2022, 44% of patients had Stage 4 cancer at diagnosis, and in the year 2021/22, 69% of individuals referred via GP services waited longer than the target of 62 days from urgent referral to treatment initiation[7]. However, these patients are often symptomatic and require rapid access to treatment. The results of these delays could be that a patient is no longer fit to receive the optimal treatment, which could ultimately increase mortality. NHS England recognises that outcomes for OG cancer should be improved and has developed a best practice 28-day timed diagnostic pathway to support NHS providers in reducing waiting times and unwarranted variation in the diagnostic process.[6] This is a valuable start, but there is still a need to address biomarker testing to support how and when decisions are made to use targeted therapy (such as ICIs). In addition, MSI-H/dMMR status may influence treatment decisions, particularly in advanced and early-stage disease.[8]

Not every OG patient requires biomarker testing. Those receiving supportive care will not receive targeted treatment, and those in the early stages of disease may be under consideration for endoscopic or surgical therapies. However, patients suitable for targeted immunotherapy will ideally have reflex (i.e. testing at diagnosis of adenocarcinoma) biomarker testing for HER2, PD-L1, and MSI-H/dMMR at the earliest practical time. In practice, NICE recommendations require an established HER2- negative status to allow access for some immunotherapies,[9,10] leading to a prioritisation of HER2 testing over other possible biomarker testing.

Biomarker testing is associated with resource use and cost, and as demand for targeted treatment grows, so will the pressure on pathology services. To ensure that oncologists have all the information needed to select a targeted immunotherapy treatment at the appropriate time, local services should consider how best to develop local testing pathways (ideally in a scalable way) to ensure that oncologists are able to initiate the most appropriate treatment at the earliest opportunity.

The aim of this study was to develop expert consensus to inform an optimal testing pathway for OG cancer care.

MATERIALS AND METHODS

The process followed a modified Delphi methodology (Figure 1) guided by the ACcurate COnsensus Reporting Document (ACCORD) checklist 2024, to develop consensus on the optimal testing pathway for OG cancer care.

In November 2023, a review of available literature on the topic of OG cancer was conducted primarily on PubMed, Google Scholar, and clinical trial registration databases. Search terms included but were not limited to: 'oesophago-gastric cancer', 'immunotherapy, 'biomarkers', 'HER2', 'PD-L1', 'histology'. A general web search using free text terms based on the inclusion criteria was also conducted to locate any additional publications relevant to this topic.

Guided by an independent facilitator (Triducive Partners Limited), a steering group of healthcare practitioners (4 consultant oncologists and 2 consultant pathologists) experienced in the diagnosis and treatment of OG cancer was gathered. These individuals were selected based on published research and experience in the testing pathway/patient selection for targeted therapies. In addition, members of the group have served on the UK-National Cancer Research Institute clinical research groups, have acted as clinical experts for NICE and RCPath (Royal College Pathology) guidelines and are members of the ESMO (European Society of Medical Oncology) and International Academy of Pathology (IAP) faculty.

The information gathered from the literature review was used to develop key questions to drive the meeting discussion. During the meeting, the steering group agreed six broad domains to develop consensus statements around:

A. Patient profile and type

B. Testing pathway ideals

C. Standards/Benchmarks

D. Optimal roles and responsibilities to improve delivery of the testing pathway

E. NHS system readiness

F. Future considerations

Each domain was discussed in turn, and 39 statements were suggested by the steering group working collaboratively. The statements were then collated, and the steering group independently rated the statements as either “accept”, “remove”, “reword”, or suggested additional statements. During the review, recommendations were accepted based on a simple majority. This constituted the initial round of consensus.

The resulting statements were developed into a Likert survey, which was distributed by a third party (M3 Global Research) in Round 2 of the process.

Recruitment of panel members was according to the following criteria:

- Currently employed in the UK NHS
- Current role of either consultant oncologist, oncology specialist nurse, oncology specialist pharmacist, or pathologist
- Experienced, or currently involved in managing of OG cancers
- Pathologists must have responsibility for at least one of the following: diagnostic histopathology and/or molecular diagnostics

Anonymity of responders was planned into the study design, and no personal information beyond the current role and UK country was captured during the survey. The identity of respondents was not known to either the steering group or facilitator. M3 Global Research provided an incentive payment of up to £32 to panellists on the completion of the survey response.

Stopping criteria were established *a priori* as a maximum of 50 responses (comprising 25 consultant oncologists, 15 consultant pathologists, 5 specialist oncology pharmacists, and 5 specialist oncology nurses), 90% of statements passing the threshold for consensus, and a threshold for consensus set at 75%, a widely accepted threshold.[11]

A statement of consent was included at the start of the survey, and consent was implied by the completion and submission of the survey. As this study only collected the anonymous opinions of healthcare professionals and no patient-specific data was captured, ethical approval was not sought.

Completed surveys were analysed to produce an arithmetic agreement score for each statement using Microsoft Excel software. The responses were aggregated to provide an overall agreement level (i.e., the number of respondents expressing agreement as a percentage of the overall number of responses for each statement). This information was then reviewed by the steering group to agree any recommendations and conclusions as a consequence.

Analysis of Round 2 was carried out in April 2024, and the second steering group meeting held two weeks later for analysis and discussion of results.

Patient and Public Involvement

None. The stated objective was to examine the opinions of experienced healthcare professionals towards the principles of an optimal testing approach for OG cancer care in the UK.

Data Availability Statement

Anonymised data is included in the supplemental materials (Figure S2).

RESULTS

During the first round of statement review with the members of the steering group, of the initial 39 statements, 3 were removed, and 5 were reworded, resulting in a final agreed set of 36 statements.

At the end of Round 2, completed questionnaires were received from a total of 50 respondents, all of which met the inclusion criteria (Table 1). Distribution of responses was as planned. The vast majority of respondents (n=47) were from England, with the remaining three from Scotland. No responses were received from Wales or Northern Ireland.

As the stopping criteria were satisfied, the steering group agreed that no further rounds were necessary.

Results from Round 2 showed very strong agreement (≥90%) in 22 (60%) statements, and strong agreement (<90% and ≥75%) in 13 (36%) of statements. The remaining one statement failed to achieve consensus (Table 1, Figure 2).

Distribution of consensus scores on the four-point Likert scale provided to respondents is represented in Figure S1.

The steering group reconvened to discuss further, agree the key points for development into a manuscript, and formulate a set of recommendations to support optimal testing in OG cancer. Both the manuscript content and recommendations were independently reviewed by the steering group prior to finalisation.

DISCUSSION

Overall, consensus agreement was achieved for all proposed statements, with the exception of Statement 9 (70%). There appears to be good awareness and desire to deliver optimal care amongst responders. It is hoped that this data can provide evidence to support the implementation of optimised testing pathways for treatment decisions in OG cancer.

Responses were received from 50 healthcare professionals working across the OG care pathway, with representation from consultant oncologists, oncology specialist nurses, oncology specialist pharmacists, and consultant pathologists. 47 of the 50 responses were from England, and no responses were received from Wales and Northern Ireland. It is, therefore, true to say that the responses largely reflect opinions from healthcare professionals in England. The conclusions and recommendations are therefore not necessarily directly applicable to practice in the other UK nations and may require local adaptation.

A. Patient profile and type

Respondents agreed (80%) that at the time of diagnosis, all patients should be tested to establish HER2, PD-L1, and MSI-H/dMMR status. This reflex testing approach (as opposed to sequential or on-demand) has the key benefit of ensuring results are available rapidly and in time for the first oncology consultation when the treatment plan is agreed. It also means that the patient may have to undergo fewer invasive biopsy procedures provided sufficient tissue is collected during diagnostic biopsy. There may be valid reasons why an individual should not be tested in this manner, such as those who are not suitable for systemic/targeted therapy. There are some key considerations for this approach that require careful planning: this approach relies on enough viable tissue being collected during biopsy, and testing all patients at diagnosis will place an increased demand on pathology services. The ideal approach is to test all patients who may receive systemic therapy for these three biomarkers at the time of diagnosis, and local services should consider what barriers exist to prevent this in practice and how these can be mitigated.

B. Testing pathway ideals

In the UK, variability exists in facilities and implementation of molecular testing services, which is dependent on local pathways and funding.[12] The Institute of Cancer Research (ICR) has stated that 'there needs to be a clearer route to the NHS for non-genomic biomarker tests, such as transcriptional, protein expression and immunohistochemistry tests' in recognition of the lack of a national system for non-genomic testing (as is in place for genomic tests). [13] This means that providers may struggle to provide reflex testing for non-genomic biomarkers at the point of diagnosis, which may delay access to targeted treatments. Both American Society of Clinical Oncology (ASCO) and European Society for Medical

Oncology (ESMO) guidelines recommend first-line treatments according to biomarker status (e.g., HER2 and PDL-1) implying that molecular testing will have been completed prior to initiation.[4,14] This picture is reflective of the strong agreed that clear guidance is needed regarding when PD-L1 testing should be carried out (S3, 92%).

Pathology services to support PD-L1 testing may be either 'in-house' at the prescribing institution, or at a centralised testing hub that serves a local provider network. Both models have advantages and disadvantages. Centralised hubs offer efficiency and consistent quality control (S4, 94%), but there are logistic considerations regarding the transport of samples for testing and turnaround times to receive results back at the prescribing institution. In-house pathology services can, in theory, provide a quicker turnaround due to the fewer logistical requirements of sending samples off-site, but setting up and maintaining a laboratory facility requires significant investment and commitment. Regardless of the specific model in place, there should be a clear agreement to ensure that results are available prior to multidisciplinary team (MDT) discussion/treatment decision making to avoid delays in treatment initiation, which could result in worsening disease (S8, 96%). Although the majority of respondents agree that ideally, testing should be conducted in-house (S6, 70%), this statement did not achieve consensus agreement. On further analysis, there was a stark difference in response by role – pathologists' agreement was 47% compared with 80% agreement for all other roles, perhaps demonstrating appreciation amongst pathologists of the effort and complexity of setting up and maintaining in-house services, or possibly that the pathologists on the responder panel were based in centralised pathology laboratories. High-levels of agreement (S9, 88%) were achieved regarding the automated transfer of biopsy tissue cores for biomarker testing, in practice this would require collection of 6-8 endoscopic biopsy cores, half of which would be sent for routine diagnostic testing and the remainder automatically transferred for biomarker testing. This would support reflex testing at diagnosis, avoid potential wastage of tissue samples, and minimise the need for re-biopsy.

There was strong agreement that reflex testing at the point of diagnosis offers benefits in reduced time to the initiation of treatment (S11, 82%), and is more cost-effective than sequential testing (S12, 80%). The responder panel very strongly supports reflex testing of all patients who are potentially suitable for systemic therapy (S13, 92%). Restricting reflex testing only to individuals suitable for systemic therapy may seem logical for HER2/PD-L1 biomarkers, dMMR/MSI-H testing is part of routine surveillance for Lynch syndrome (which is a cause of gastric cancer) and so testing all diagnosed patients for HER2, PDL-1, MSI-H and dMMR may be valuable when patients progress in their disease. This approach would mean testing patients who will not go on to receive targeted therapy, but this may be beneficial to the efficiency of the treatment pathway overall and certainly to those patients who do go on to require such treatment and are not faced with delays due to a lack of biomarker characterisation. Whilst no direct evidence exists regarding the cost-effectiveness of reflex testing in OG cancer, evidence does exist to support reflex testing approaches in other cancers. Gosney et al[15] investigated the cost-effectiveness of pathologist-initiated reflex testing in non-small-cell lung cancer (NSCLC). They concluded that timely biomarker testing is crucial for selecting first-line systemic therapy for patients, and reflex testing is expeditious and standardises the ordering of biomarker tests. The authors suggest that reflex testing

must be governed by an MDT-defined protocol, and that this protocol requires collaboration between MDT and policymakers to ensure compliance with the latest guidelines and reimbursement criteria. A retrospective cohort study of newly diagnosed stage IV non-squamous NSCLC patients found that implementation of a reflex molecular testing pathway increased the proportion of patients who underwent comprehensive tissue-based molecular testing upon initial diagnosis.[16] Ideally, an audit or retrospective study addressing the cost-effectiveness/efficiency of using reflex vs sequential testing in OG cancer is needed to demonstrate logistical, time-to-treatment, or patient outcome gains in order to provide support for local business cases.

Intratumour, spatial (between baseline primary and metastatic tumours) and temporal (between tumour before and after chemotherapy) heterogeneity is well known in Upper GI cancers. Discrepancies rates have been reported in up to 33% of cases between primary and metastatic deposit and concordance rates between tumours before and after chemotherapy varied between 57-63% of cases.[17,18] In addition in view of the risk of false negative scoring if only a single biopsy is taken, several groups have suggested that multiple biopsies (at least 6) are recommended for accurate diagnosis, biomarkers and molecular analysis of upper GI cancer.[4] Although it has been suggested that multiple biopsies of primary and metastatic sites might need to be tested before considering treatment options, there are no consensus guidelines to recommend testing of metastatic deposit of re-biopsy after neo-adjuvant therapy if the diagnostic biopsy was PD-L1 negative.

C. Standards/Benchmarks

Here, 94% of respondents agreed that biomarker tests should be turned around within 10 working days (S14), but a lower agreement was achieved regarding the return of results within 5 working days from receipt of the sample by the pathology lab (S15, 78%). Whilst this may not reflect the current capability of in-house pathology services, it should be the aspiration to deliver this level of service and funding should reflect this growing need. Pathologists exhibited only 47% agreement with S15, perhaps as they are aware of the logistical challenges in delivering results within 5 days. There is a need for clear UK standard guidelines regarding how a realistic turnaround time (perhaps 10 days in line with S14) can be achieved agnostic of laboratory setting. These guidelines should also stipulate that the laboratory facility must be the International Standards Organisation (ISO) 15189 United Kingdom Accreditation Service (UKAS) approved (S16, 94%). The external assurance framework for pathology services is based on both external quality assurance (EQA) and UKAS. The laboratory facility must therefore relevant EQA annual subscription (where available) and must obtain adequate scores during this process.[19]

Respondents agree that from request to results, the testing process is often delayed by logistical issues (S17, 76%). The response by role is interesting as oncologists were the only role group with a response above the consensus threshold (84%), suggesting that if responder numbers were equal amongst these groups, then this statement would not have achieved consensus.

The key aim for optimising the testing pathway is to ensure that all relevant information is available to the MDT/oncologist to allow for the most appropriate treatment to be recommended from the outset. This currently includes HER2, PD-L1, and MSI-H/dMMR status but is likely to expand as new targeted/biomarker driven therapies become available in the future. This should be accepted as the 'gold standard' for OG cancer care. The NHS England best practice timed pathway[6] proposes a 28-day period from referral through diagnosis to the first outpatient clinic; biopsy to support diagnosis is scheduled within 7 days, once the diagnosis is confirmed (by Day 14) there is a 14-day window for biomarker status testing provided appropriate samples can be collected at biopsy.

D. Optimal roles and responsibilities to improve delivery of the testing pathway

There was very strong agreement that a lack of coordination between disciplines can impact the testing pathway (S24, 96%), and that a dedicated coordinator should be in place to manage the test process from request to results dissemination (S25, 84%). The role of the MDT is pivotal in ensuring that treatment is planned appropriately, and the National Institute for Health and Care Excellence (NICE) Oesophago-gastric cancer Quality Standards define the core roles of the full MDT, but this can be augmented as needed.[20]

If results of biomarker testing are to be available for the 1st outpatient appointment with the oncologist, an efficient process must be implemented to minimise any potential logistical delays. The MDT should agree, document, and implement and audit appropriate performance measure (key performance indicators/KPIs) for the OG testing pathway to identify where delays occur and to modify the pathway to release these bottlenecks. Performance data can also be used to support business cases for improvements to the pathway and quantify the impact of making improvements versus the current status quo.

E. NHS system readiness

Results from this section demonstrate that there is strong agreement that the NHS and industry should work more collaboratively in horizon scanning of future technologies. This would provide a greater opportunity for the NHS to put services in place to support new technologies and also agree requirements to manage capacity according to anticipated demand for specific technologies (e.g., use of Dako versus Ventana technologies for biomarker testing). There is also potential for NHS pathology services to explore how the use of artificial intelligence (AI) might improve diagnostic efficiency – as is being realised in other therapy areas.[21,22]

As part of 'future readiness', educational programmes should be in place for all MDT roles at the earliest practical point to support clinical decisions (S31, 96%).

It is also important that the NHS and NICE agree that when a technology is undergoing appraisal for cost-effectiveness, the costs of processes that are essential for meeting the reimbursement criteria (as set out by NICE) are packaged as part of the reimbursement package (S34, 98%). This is to avoid the situation where the availability of funding for diagnostic tests may act as a potential barrier to expediting recommended treatment initiation.

Strengths and limitations

All statements (with one exception) achieved consensus agreement, suggesting either that the responders recognise and agree with the perspectives of the steering group, or that the statements were (unconsciously) designed to be agreeable – indicating potential bias. There was a difference in number of responses sought from oncologists (n=25) and pathologists (n=15). The steering group suggested and agreed these numbers at the first meeting, however, given some of the differing responses to some of the statements by these groups, an equal representation (both n=20) may have provided a more equitable representation and led to a difference in the achieved results, signifying a methodological limitation. In addition, a larger total cohort of responders would have provided greater certainty that the opinions expressed were representative of each individual role.

The responses from outside of England were low, with only 3 responses from Scotland and none from Wales or Northern Ireland, potentially reducing the applicability of the recommendations made here to these health systems. There is a clear need to understand the opinions of healthcare professionals in the devolved nations to provide a comparison and extend the remit of this work and further work should be focused on this. As a consequence, where policy and reimbursement have been discussed, the focus had been kept on the NHS in England to represent the responder demographic.

The patient experience has not been investigated (as it was outside of the scope of the study objectives), but it would be valuable in providing feedback on how problems in the current testing pathway can impact the individual, and, also, what steps in the process that patients consider a priority.

RECOMMENDATIONS

Based on the survey results and subsequent discussions within the steering group, the authors propose the following recommendations to support treatment decisions in OG cancer. A proposed diagnostic pathway that reflects the recommendations is included in Figure 3.

1. All patients suitable for systemic therapy should be tested for HER2, PD-L1, and MSI-H/dMMR at the time of diagnosis
2. A dedicated coordinator should be in place to plan, request, and coordinate dissemination of test results

3. Results of biomarker testing should be available within 10 days of request
4. All tests should be conducted by an approved United Kingdom Accreditation Service (UKAS) laboratory
5. Automatic transfer of specific tissue cores should be in place for centralised processing
6. All test results should be made available on a single, integrated report
7. All test results should be with the MDT/oncologist prior to the first consultation post-diagnosis
8. Treatment should be initiated within 30 days of receiving biomarker test results at the latest
9. All testing pathways should have MDT agreed KPIs in place and tracked for audit purposes
10. Funding and reimbursement routes for mandatory diagnostic tests should be bundled with any NICE-approved treatments

To facilitate implementation of these recommendations, local services may need to construct a business case to ensure funding is in place for reflex testing (and associated pathology resource requirements). Providers should also engage with NHS and NICE regarding the potential for national provision of molecular testing as is currently in place for genomic testing.

CONCLUSION

This modified Delphi exercise was able to achieve agreement from a panel of 50 experts currently involved in OG cancer for 35 of 36 statements. In this paper we have described the current heterogeneity that exists in the UK NHS regarding the provision of molecular pathology in OG cancer, the results demonstrate clear recognition amongst responders of the need for clarity and standardisation of the testing pathway for OG cancer. These recommendations are designed to set a minimum bar for OG cancer services to ensure greater concordance between providers in patient experience and access to licensed and guideline-recommended treatments.

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SUPPLEMENTAL INFORMATION

Supplemental Figure (S1)

Anonymised Results Data

DECLARATIONS

This study did not require registration because neither the assigned interventions nor the outcomes assessed were related to the health of participants.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

FUNDING

MSD pharmaceuticals initiated and supported this consensus project including the selection of faculty of experts. MSD paid the expert group honorarium. MSD commissioned Triducive Ltd (UK) to facilitate the project and analyse the responses to the consensus statements, in line with Delphi methodology. MSD had no input into drafting or publication of the manuscript.

CONFLICTS OF INTEREST

All authors received honoraria from MSD while undertaking this study. MSD commissioned Triducive Partners Limited to facilitate the project and analyse the responses to the consensus statements in line with the Delphi methodology.

Author declarations:

ME has received sponsorship from MSD to attend an international conference and honoraria from MSD and BMS and Servier for advisory work. **MR-J** has received honoraria for attendance at advisory boards, chairing educational meetings, consultancy, travel, accommodation and registration at national/international meetings from BMS, MSD, Roche Diagnostics Solutions, Agilent, Ibex Medical and research/educational grants from Pfizer and Roche Diagnostics Limited. **NS** has received honoraria for attendance at advisory boards, consultancy, travel, accommodation and registration at national/international meetings from Servier, GSK, Takeda, BMS, Merck, MSD, Pierre Fabre, Astellas, Natera, Daiichi Sankyo and Tempus. NS has also received research/educational grants from Gilead.
PT has received honoraria for attendance at advisory boards, consultancy, travel, accommodation and registration at national/international meetings from Agilent, AstraZeneca, Bristol-Myers Squibb, Lilly, Merck Serono, MSD, Novartis, Pfizer, Roche, Takeda, Janssen, Biocartis, Diaceutics, Astellas. **TB** has received lecture fees from MSD, AstraZeneca and Elekta, and consulting fees from MSD. **WM** has received honoraria for attendance at advisory boards, consultancy, travel, accommodation and registration at national/international meetings from Amgen, BMS, Beigene, Pfizer , MSD, Servier and BMS.

AUTHORS' CONTRIBUTIONS

All views expressed by the authors are those of the individual and do not represent those of their organisation/place of work. Contributors MRJ, WM, TB, ME, NS, PT agreed the design of the study, formulated and reviewed the statement set. Results of the study were discussed by all contributors as part of a formal Steering Group meeting where commentary was agreed for development into the initial draft manuscript. MRJ, WM, TB, ME, NS, PT took an equal role

in reviewing the initial manuscript draft and providing comments, and all approved the final draft. MRJ is the guarantor for the work and/or conduct of the study, had access to the data and controlled the decision to publish.

ACKNOWLEDGEMENTS

The authors wish to thank Tim Warren and Ian Walker from Triducive Partners Limited for their support in collating the data, analysing the results, drafting the initial manuscript, and reviewing the final draft. This project was initiated & funded by MSD UK Ltd.

TABLES AND FIGURE LEGENDS

Table 1. Defined consensus statements and corresponding levels of agreement

No:	Statement:	Strongly Agree	Tend To Agree	Tend To Disagree	Strongly Disagree	Overall Agreement
Domain A: Patient profile and type						
1	All patients should be tested for HER2, PD-L1 and MSI-H/dMMR at time of diagnosis	46%	34%	6%	14%	**80%**
2	All patients considered potentially suitable for systemic therapy should be tested for HER2, PD-L1 and MSI-H/dMMR	64%	26%	0%	10%	**90%**
Domain B: Testing pathway ideals						
3	There is a need for clear guidance on which stage of the pathway PD-L1 testing should be used	44%	48%	2%	6%	**92%**
4	A centralised, testing service can provide more efficiency and quality control in the service	42%	52%	2%	4%	**94%**
5	PD-L1 testing should be completed in advance of MDTs to inform decision making	42%	44%	10%	4%	**86%**
6	Ideally, testing should be conducted within the prescribing institution	24%	46%	26%	4%	**70%**
7	Variance in the testing pathway leads to delays in patients accessing appropriate treatment	32%	58%	8%	2%	**90%**
8	A delay in the diagnostic process may potentially prevent optimal treatment entirely if the patient's disease worsens significantly	48%	48%	2%	2%	**96%**
9	It would be beneficial for automatic transfer of specific tissue cores to be in place for centralised processing	38%	50%	10%	2%	**88%**
10	Treating physicians need to be informed promptly when there is insufficient tissue to satisfy testing requirements and so re-biopsy may be indicated	66%	30%	2%	2%	**96%**
11	Reflex testing at the point of diagnosis is more efficient than sequential testing and may reduce the time to initiation of treatment	38%	44%	16%	2%	**82%**
12	Reflex testing at the point of diagnosis is more cost-effective than sequential testing	30%	50%	16%	4%	**80%**
13	Reflex testing at the point of diagnosis is recommended in all patients considered potentially suitable for systemic therapy	46%	46%	2%	6%	**92%**
Domain C: Standards/Benchmarks (inc. reference centre v in-house testing v regional hubs)						
14	Biomarker tests should be turned around within 10 working days	42%	52%	2%	4%	**94%**

15	Results of biomarker tests should be available no longer than 5 working days from the day the sample arrives at the pathology laboratory	30%	48%	12%	10%	**78%**
16	Either in-house or outsourced, tests need to be delivered by an approved United Kingdom Accreditation Service (UKAS) laboratory	52%	42%	4%	2%	**94%**
17	The process from requesting a test to receiving the results is often unduly delayed by logistical issues	32%	44%	20%	4%	**76%**
18	All test results should be made available on a single, integrated report	50%	40%	8%	2%	**90%**
19	All test results should be with the oncologist prior to the first consultation post-diagnosis	48%	38%	10%	4%	**86%**
20	If there is insufficient tissue for biomarker testing, this should be discussed at the MDT	48%	48%	2%	2%	**96%**
21	Treatment should be initiated within 30 days of receiving biomarker test results	46%	44%	8%	2%	**90%**
22	Positivity rates should be audited for the specific PD-L1 assay for comparison with literature-reported rates	42%	52%	4%	2%	**94%**
Domain D: Optimal roles and responsibilities to improve delivery of the testing pathway						
23	Clearly defined roles and responsibilities for each stage in the testing pathway would benefit the efficiency	44%	52%	2%	2%	**96%**
24	Lack of co-ordination between disciplines involved in the testing pathway can limit efficiency of the process	38%	56%	4%	2%	**94%**
25	A dedicated coordinator should be in place to plan, request, and coordinate dissemination of the results of tests	40%	44%	14%	2%	**84%**
26	The MDT is responsible for ensuring that the correct testing pathway is in place	48%	38%	10%	4%	**86%**
27	The testing pathway should have agreed and documented time and KPI targets	36%	52%	8%	4%	**88%**
28	Testing pathway performance should be measured by the MDT	34%	44%	18%	4%	**78%**
29	Business cases can benefit the establishment of consistent testing pathways that are efficient and accessible	38%	56%	4%	2%	**94%**
Domain E: NHS system readiness						
30	Collaborative horizon scanning between NHS and industry would be beneficial to help NHS readiness	30%	68%	0%	2%	**98%**
31	Education of the entire MDT is vital to improve NHS system readiness for new tests and treatment modalities	54%	42%	2%	2%	**96%**
32	Any advent of technology and testing use needs to consider capacity concerns in the NHS	50%	46%	2%	2%	**96%**
33	Any advent of technology and testing use needs to consider resource requirements rather than just acquisition costs	46%	34%	6%	14%	**94%**
34	NHS and NICE need to work more collaboratively so when new therapies are approved there is resource in the NHS provision for the accompanying biomarker test	64%	26%	0%	10%	**98%**
Domain F: Future considerations						
35	A coordinated industry group to liaise with NHS and policy makers could help support future utilisation of new tests and modalities	44%	48%	2%	6%	**92%**
36	Artificial Intelligence technologies have the potential to improve the speed with which test results are analysed and processed	42%	52%	2%	4%	**88%**

Figure 1. Modified Delphi study design

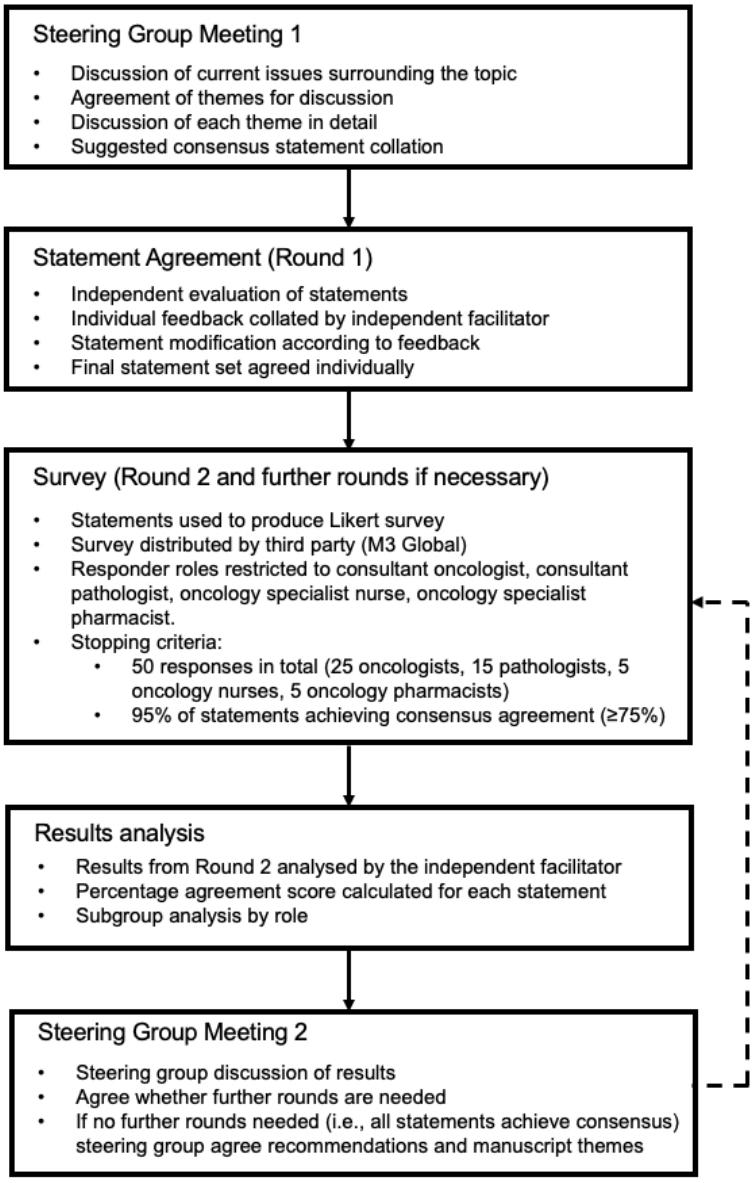
Figure 2. Consensus agreement levels by statement. The threshold for consensus is depicted by the green line (75%). The blue line signifies the threshold for very strong agreement (90%)

Figure 3. Potential diagnostic pathway and indicative timescales. Based on consensus results and NHS England 28-day best practice timed pathway[6]

Supplemental figures

Figure S1. Percentages of agreement level by statement

Figure S2. Consensus Survey Results Data



Modified Delphi study design

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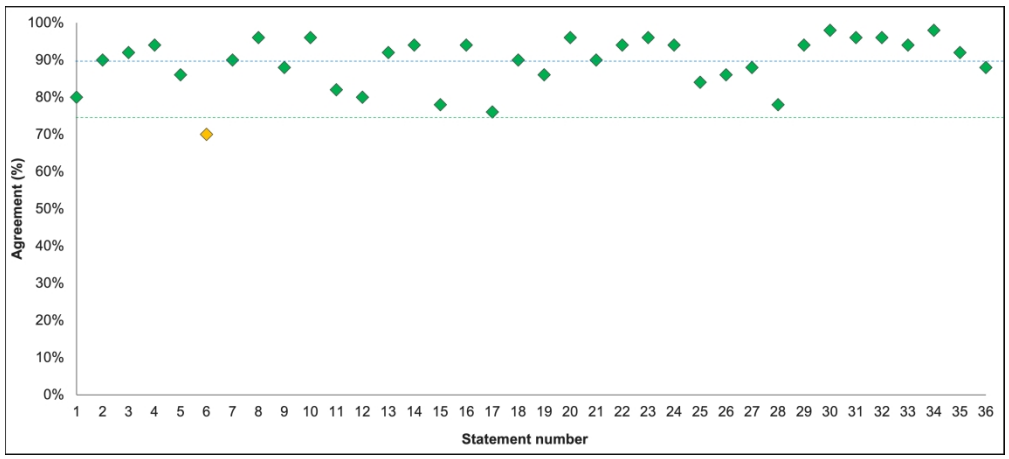


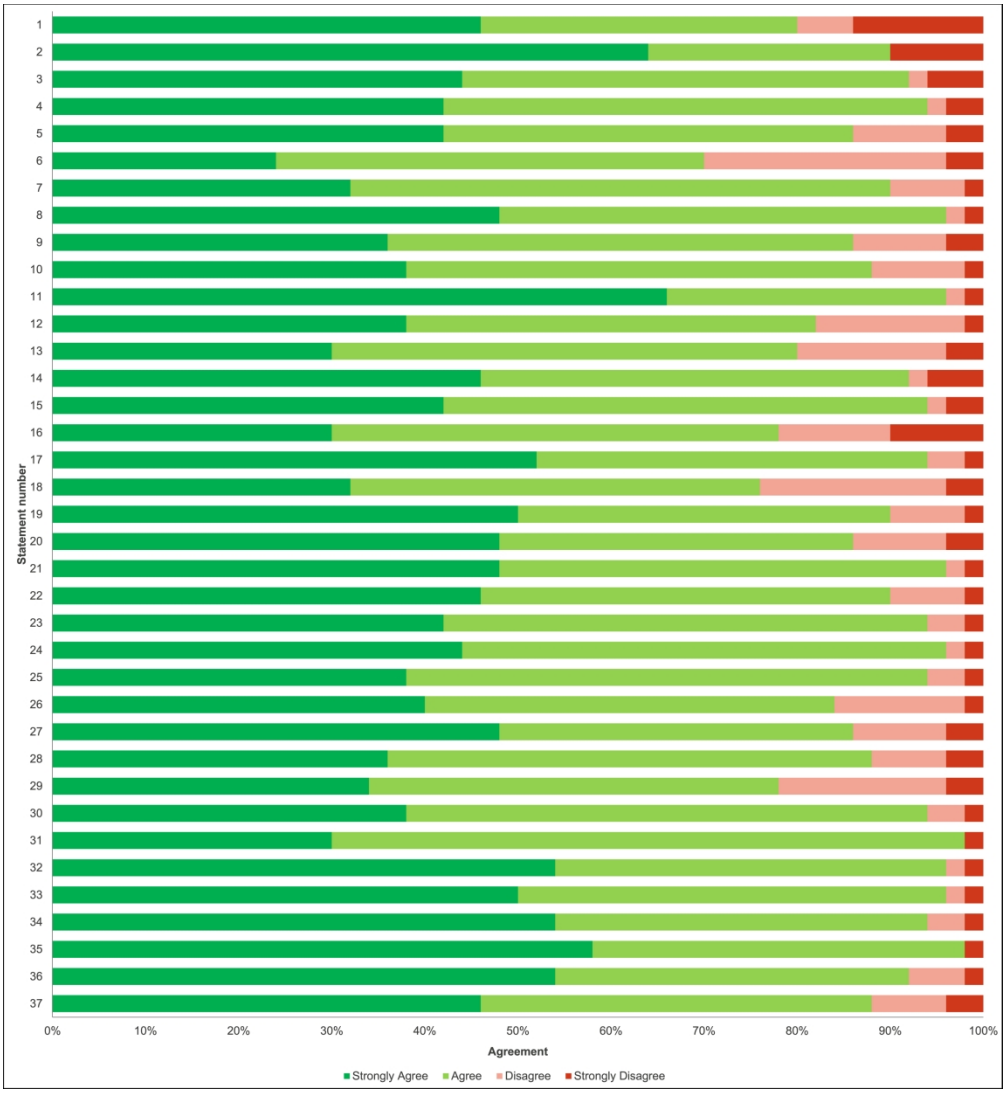
Consensus agreement levels by statement. The threshold for consensus is depicted by the green line (75%). The blue line signifies the threshold for very strong agreement (90%)

392x175mm (330 x 330 DPI)

Diagnosis			MDT	1st Outpatient Clinic
Day 0	Day +3	Day +4	Day +10	Day +18
Oesophago-gastro-duodenoscopy (OGD) to BSG/AUGIS quality standards Trans-nasal endoscopy (TNE) Whole-body CT scan Biopsy samples taken to support molecular testing	Diagnostic histology results reported	F-18 FDG PET-CT (within 24 hours) for those suitable for radical treatment (except for T1a tumours) +/- endoscopic ultrasound +/- staging laparoscopy Reflex biomarker tests requested for HER2, PD-L1, MSI-H/dMMR for those who may receive a targeted therapy	Specialist MDT Results of biomarker testing reported in 1 standardised report	Outpatient clinic Assessment of fitness to treat Agree personalised treatment plan Patient optimisation

Potential diagnostic pathway and indicative timescales. Based on consensus results and NHS England 28-day best practice timed pathway6

711x407mm (72 x 72 DPI)



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		ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50
		Specialty (1=Consultant Oncologist, 2=Consultant Pathologist, 3=Specialist Oncology Nurse, 4=Specialist Oncology Pharmacist)	4	4	3	1	1	1	1	1	3	3	1	1	1	4	1	1	4	4	3	1	1	2	1	1	1	1	1	1	2	2	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2
	Pathologist specific focus	Histopathology																						1							1	1									1	1	1	1	1	1	1	1	1	1	1	1	1
		Molecular Diagnostics																						0							0	0									0	0	0	0	1	0	0	0	0	1	1	1
		Coagulation																						0							0	0									0	0	0	0	0	0	0	0	0	0	0	0
		Haematology																						0							0	0									0	0	0	0	0	0	0	0	0	0	0	0
		Immunology																						0							0	0									0	0	0	0	0	0	0	0	0	0	0	0
		Toxicology																						0							0	0									0	0	0	0	0	0	0	0	0	0	0	0
		None of the above																						0							0	0									0	0	0	0	0	0	0	0	0	0	0	0
		Are you currently involved with, or do you have experience with, oesophago-gastric canc	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Do you have experience testing for PDL1 in oesophago-gastric cancers?																						Y							Y	Y									Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Where is your primary place of work? (1=England, 2=Scotland, 3=Northern Ireland, 4=Wales)	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1
		What is the estimated number of cases of oesphago-gastric cancer do you see each year? (1=<20, 2=20-50, 3=>50)	3	3	3	2	1	1	2	3	3	3	2	3	2	3	2	2	2	1	3	3	3	3	3	2	2	2	2	3	3	2	2	2	2	3	3	3	3	3	2	2	2	3	1	2	1	1	2	3	2	2
Statement number (1=Strongly Disagree, 2=Disagree, 3=Agree, 4=Strongly Agree)	1	All patients should be tested for HER2, PD-L1 and MSI/DMMR at time of diagnosis	3	4	4	4	4	1	3	4	1	4	3	4	3	4	3	2	3	1	3	3	4	4	4	1	3	4	3	4	4	4	1	2	4	4	4	3	4	4	4	3	4	1	3	4	3	3	1	4	2	4
	2	All patients considered potentially suitable for systemic therapy should be tested for HER	4	4	4	4	4	1	4	4	1	4	3	4	4	4	4	4	4	3	1	3	3	4	4	4	3	4	3	4	4	4	4	4	4	3	4	4	3	4	4	4	3	4	1	3	4	3	3	1	4	4	4
	3	There is a need for clear guidance on which stage of the pathway PD-L1 testing should b	3	3	4	3	4	3	3	4	1	4	4	3	4	4	4	4	4	4	1	3	3	3	2	3	3	1	3	3	4	3	4	4	4	3	4	4	4	4	3	4	3	4	3	4	3	4	3	4	3	3
	4	A centralised, testing service can provide more efficiency and quality control in the servic	3	4	4	4	3	4	3	3	1	4	3	4	3	4	4	3	3	3	4	3	4	4	1	3	4	3	3	4	3	3	3	4	3	3	4	3	3	3	3	4	3	3	3	2	4	3	4	4	4	4
	5	PD-L1 testing should be completed in advance of MDTs to inform decision making	2	4	4	4	3	4	4	3	1	4	4	3	4	4	3	3	3	3	4	3	4	4	4	2	4	3	2	4	1	3	4	4	3	4	4	3	3	4	3	3	3	2	3	4	2	3	3	3	3	3
	6	Ideally, testing should be conducted within the prescribing institution	4	4	4	4	2	3	4	4	3	1	4	3	3	3	2	3	3	3	3	4	3	3	2	4	3	4	3	3	4	1	2	3	3	3	4	2	2	4	3	2	3	2	3	3	2	3	3	2	2	3
	7	Variance in the testing pathway leads to delays in patients accessing appropriate treatm	3	4	4	3	3	4	3	4	1	4	3	4	3	3	2	3	3	2	3	3	3	3	4	3	4	3	4	3	3	4	3	4	4	3	4	4	4	4	4	3	4	3	3	3	3	3	4	2	3	3
	8	A delay in the diagnostic process may potentially prevent optimal treatment entirely if the	4	4	4	4	4	4	3	3	1	4	2	3	3	4	3	4	3	3	3	3	4	3	4	3	4	3	3	4	3	3	4	4	4	4	4	4	4	4	4	4	3	3	4	3	3	3	3	4	3	3
	9	It would be beneficial for automatic transfer of specific tissue cores to be in place for cen	3	3	4	4	4	4	3	3	1	4	4	3	4	3	4	3	4	3	3	3	3	3	4	4	3	4	4	3	3	4	2	3	3	4	4	4	4	4	3	4	2	2	3	2	3	3	3	2	4	3
	10	Treating physicians need to be informed promptly when there is insufficient tissue to sati	4	4	4	4	4	4	4	4	1	4	3	3	4	4	4	4	4	4	3	3	4	4	4	2	4	3	3	4	4	4	4	4	4	3	4	3	3	4	4	3	4	4	3	4	4	3	4	3	4	4
	11	Reflex testing at the point of diagnosis is more efficient than sequential testing and may	3	3	4	4	4	3	3	4	1	4	3	4	2	3	4	3	3	3	3	3	3	2	4	4	4	3	3	3	4	2	4	4	3	3	4	2	2	4	3	3	4	4	2	4	3	3	4	2	4	3
	12	Reflex testing at the point of diagnosis is more cost-effective than sequential testing	2	2	4	4	4	4	3	4	1	4	3	4	2	3	3	3	3	3	3	3	3	4	4	2	3	3	2	4	1	3	4	4	3	2	4	3	3	3	3	3	4	4	2	4	3	3	3	4	2	3
	13	Reflex testing at the point of diagnosis is recommended in all patients considered poten	3	3	4	4	4	4	3	4	1	3	4	4	1	3	3	3	3	3	3	3	4	4	4	3	3	3	3	4	1	4	4	4	4	4	4	4	4	4	4	3	3	4	4	2	4	3	3	4	4	3
	14	Biomarker tests should be turned around within 10 working days	3	3	3	3	3	4	3	4	1	3	3	3	4	4	4	3	2	4	3	3	4	3	4	3	3	3	4	4	3	3	4	4	4	4	4	4	4	3	1	3	4	3	3	4	3	4	4	4	4	4
	15	Results of biomarker tests should be available no longer than 5 working days from the d	3	4	4	4	3	3	4	4	1	4	3	3	3	3	4	3	3	1	3	3	3	2	4	2	3	3	4	3	3	4	1	2	3	3	4	3	3	4	3	2	2	1	3	2	3	3	3	1	4	4
	16	Either in-house or outsourced, tests need to be delivered by an approved United Kingdo	3	4	4	4	3	3	3	4	1	4	4	3	4	4	4	3	3	3	4	3	4	4	4	3	3	3	3	3	4	4	4	4	4	4	4	3	3	3	4	4	3	4	4	4	4	3	4	4	4	3
	17	The process from requesting a test to receiving the results is often unduly delayed by log	2	3	3	3	3	2	3	4	1	4	4	4	3	4	2	3	2	3	2	3	4	1	4	2	2	3	3	4	2	3	4	4	4	4	4	4	4	4	4	3	4	4	3	3	3	2	3	4	3	3
	18	All test results should be made available on a single, integrated report	3	4	4	4	2	4	3	4	1	4	3	3	4	4	4	3	3	3	3	3	4	3	4	4	4	3	3	4	3	4	4	4	4	2	4	3	3	3	2	4	3	2	4	4	4	4	2	3	4	4
	19	All test results should be with the oncologist prior to the first consultation post-diagnosis	3	4	3	4	3	4	3	4	1	4	4	2	3	3	4	3	2	4	3	3	4	4	4	2	4	3	3	4	2	4	3	3	4	1	3	4	2	3	4	4	3	4	1	3	4	2	3	4	3	3
	20	If there is insufficient tissue for biomarker testing, this should be discussed at the MDT	4	4	4	4	3	4	4	4	3	1	4	3	3	3	3	3	4	3	3	3	3	4	4	4	3	2	3	4	4	4	3	3	4	3	4	4	4	4	4	3	4	3	4	3	4	3	3	3	3	4
	21	Treatment should be initiated within 30 days of receiving biomarker test results	4	4	4	4	4	4	3	3	1	4	2	4	4	4	4	3	3	4	3	3	3	2	4	4	4	3	3	4	3	3	3	4	2	4	4	3	3	4	3	3	4	2	3	4	4	3	3	3	4	3
	22	Positivity rates should be audited for the specific PD-L1 assay for comparison with literat	3	4	4	4	3	3	3	4	1	4	4	3	2	3	4	3	3	3	3	3	3	3	4	3	4	3	3	4	3	3	2	2	3	4	4	3	3	3	4	4	3	4	3	4	4	3	3	4	4	4
	23	Clearly defined roles and responsibilities for each stage in the testing pathway would be	4	4	4	4	3	4	3	3	1	4	3	4	4	4	4	3	3	4	3	3	3	3	4	3	4	3	3	4	3	3	3	4	3	3	4	4	4	4	3	3	4	4	3	4	4	3	3	3	4	3
	24	Lack of co-ordination between disciplines involved in the testing pathway can limit efficie	3	4	4	4	3	3	3	3	1	4	3	4	4	4	3	3	4	4	3	3	3	3	4	3	3	3	3	4	3	3	4	4	4	3	4	4	3	3	3	3	4	4	3	3	4	4	3	3	3	4
	25	A dedicated coordinator should be in place to plan, request, and coordinate disseminati	2	3	4	3	3	4	3	4	1	4	4	4	4	3	4	3	3	3	4	3	3	3	4	2	3	3	3	4	2	2	3	4	4	4	2	4	4	3	3	4	2	3	4	3	3	3	3	4	2	2
	26	The MDT is responsible for ensuring that the correct testing pathway is in place	2	4	3	4	3	4	3	4	1	4	4	1	4	3	2	3	3	4	4	3	4	4	4	2	3	3	3	3	4	3	4	4	3	4	4	4	4	4	3	4	4	4	2	3	4	3	3	4	2	3
	27	The testing pathway should have agreed and documented time and KPI targets	3	4	3	4	4	3	4	4	1	4	3	2	4	3	4	3	3	3	4	3	4	3	4	2	4	3	3	4	2	3	4	4	3	2	4	3	3	3	3	4	4	1	3	4	3	3	3	3	3	3
	28	Testing pathway performance should be measured by the MDT	2	2	3	4	3	4	4	4	1	4	4	3	4	3	4	3	3	3	3	2	3	4	2	4	2	2	2	3	3	4	2	3	4	3	4	4	4	4	3	3	3	4	1	3	4	2	3	3	3	2
	29	Business cases can benefit the establishment of consistent testing pathways that are effi	3	4	4	3	4	2	3	3	1	4	4	3	4	4	3	3	3	4	4	3	4	3	4	3	3	3	3	4	3	3	3	4	3	3	4	4	4	3	3	4	3	3	4	3	3	4	3	3	4	3
	30	Collaborative horizon scanning between NHS and industry would be beneficial to help f	3	4	4	3	3	4	3	3	1	3	3	4	3	4	3	3	3	3	4	3	3	3	4	3	4	3	3	3	3	3	3	3	3	3	4	4	4	4	3	3	3	3	3	4	3	4	4	3	4	3
	31	Education of the entire MDT is vital to improve NHS system readiness for new tests and	3	4	4	4	4	4	4	3	1	4	4	3	3	4	4	3	3	3	4	4	3	4	4	4	4	4	3	3	3	3	3	2	3	4	4	3	4	3	3	4	4	4	3	4	3	3	4	4	4	3
	32	Any advent of technology and testing use needs to consider capacity concerns in the NH	3	4	3	4	3	3	4	4	1	4	3	3	3	4	4	3	3	3	4	4	3	4	4	4	4	4	3	3	3	4	4	3	3	4	4	3	3	4	3	3	3	3	3	4	3	4	4	2	3	3
	33	Any advent of technology and testing use needs to consider resource requirements rath	3	4	4	3	3	3	4	4	1	3	3	2	4	4	4	3	3	4	4	3	3	3	4	4	4	3	4	3	3	4	4	4	4	3	2	4	4	4	3	3	4	4	4	3	4	4	3	4	4	4
	34	NHS and NICE need to work more collaboratively so when new therapies are approved	3	4	4	4	4	4	3	4	1	4	4	3	4	4	3	3	3	4	4	3	4	3	4	4	3	4	3	3	4	4	4	4	4	3	4	4	4	3	3	3	4	4	4	4	4	3	3	4	4	3
	35	A coordinated industry group to liaise with NHS and policy makers could help support fu	2	4	4	4	4	3	3	4	1	4	3	4	4	4	4	3	3	4	4	3	4	2	4	3	4	3	3	4	2	3	4	4	4	4	4	4	3	4	3	3	4	4	3	4	3	3	3	4	4	3
	36	Artificial Intelligence technologies have the potential to improve the speed with which te	3	4	4	3	3	2	4	3	1	4	4	3	4	3	2	3	4	4	3	3	4	3	1	3	4	3	3	4	2	2	4	4	4	4	4	3	3	4	4	3	4	4	3	4	3	4	3	3	4	4