# Project DELTA –

# integrateD diagnostic solution for EarLy deTection of oesophageal cAncer

# Round Table Discussion Report:

## Does the Cytosponge have a role in symptomatic patients?

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**Date of Event: 25th February 2021**

# 1. Contents

# 1. Executive Summary

The Cytosponge-TFF3 test is a diagnostic technology developed by Professor Rebecca Fitzgerald's team aimed at diagnosing Barrett's Oesophagus. It can also be used to detect other oesophageal conditions and with the use of additional biomarkers it can identify dysplasia and cancer.

There are number of considerations to take into account on how, where and when to use Cytosponge TFF3. A 'round table' discussion was held to discuss how best to implement the Cytosponge-TFF3 into clinics.

There is a general consensus in favour of using the Cytosponge as a triage tool for endoscopy referral. The Cytosponge would be offered within an integrated environment that promotes its use as a triage tool. A further suggestion was to conduct some prospective studies to stratify and use Cytosponge as a 'rule out test'.

# 2. Introduction

The Cytosponge-TFF3 test has been shown to be safe and acceptable to patients in studies involving >4,000 individuals across 3 continents. Additionally, a randomised trial of over 13,000 eligible individuals has just been successfully completed, verifying it's safety. (1,2)

There are several potential ways in which the Cytosponge can be implemented into routine care for symptomatic individuals. The bulk of the evidence of its success has been accrued for patients in primary care on medication for reflux, who are approached proactively to have a test (targeted screening). There is also consideration being given to using Cytosponge-TFF3 test as a diagnostic test for patients with reflux symptoms (no alarm symptoms) as a triage for endoscopy in either the primary or secondary care setting. (3–5)

There are a number of considerations that need to be taken into account before moving from the screening to the diagnostic setting. For example, patient and clinician preferences, endoscopy waiting lists, potentially missed pathology and the ability to include appropriate safety netting.

The methods, findings, conclusions and recommendations resulting from the round table discussion are detailed in the following report.

# 3. Methods

## 3.1 Organising the event

This round table event was conducted on 25th of February 2021 where gastroenterologists, academic GPs, practicing GPs, Pathologists, NHS commissioners were invited to participate. This group of specialities was selected in order to bring a variety of perspectives on the role of Cytosponge in the healthcare systems of UK.

The event started at 12.00 pm with opening remarks from Professor Peter Sasieni (PS) from King's college London, collaborator on the DELTA project and chair for the event.

Massimiliano Di Pietro (MDP) from Cambridge then presented on "Background of the Cytosponge and Oesophageal and Gastric pathology" and Oliver Stovin (OS), Macmillan GP from Cambridge presented on "How the Cytosponge could fit into Primary care?"

After the break, two breakout sessions took place as planned, where the participants were divided into 2 groups and participated in two sessions where given topics were discussed. In the first session the topic of discussion was "Cytosponge for proactive case-finding in primary care" and the topic of discussion for the second session was "Symptomatic referrals in primary care".

After the breakout sessions, all participants joined together again to feedback on the breakout sessions contributing towards the plenary discussion. The meeting was concluded by closing remarks from the chair, Professor Peter Sasieni.

All discussions during the round table event (including breakout rooms) were recorded using Zoom recording.

### 3.2 Analysis of transcripts

The zoom recordings of the breakout sessions were transcribed using the software 'Rev'. Manual corrections were carried out to tally the videos with the transcript.

The following steps were followed to form this report -

Reading and listening the interviews several times to become familiar with the context of the discussions.

Themes were identified to categorise reoccurring words, phrases and issues. This allowed these common words, phrases and issues to be organised and translated into the findings. The themes identified were:

- Use of Cytosponge-TFF3 in Primary care
- Use of Cytosponge-TFF3 in Secondary care
- Use of Cytosponge-TFF3 as a triage test
- Cytosponge-TFF3 as a rule in test
- Cytosponge-TFF3 as a rule-out test.

## 4. Findings

Very extensive and useful discussions on the use of the Cytosponge-TFF3 test in the primary and secondary care settings took place during the round table discussions. In summary these discussions included whether the Cytosponge TFF3 could be used as a rule-in, rule-out test or, as a diagnostic tool for diagnosis of gastric disorders.

The findings of the discussions are listed –in sections 4.1 – 4.3.

### 4.1 Studies about the use of Cytosponge TFF34

An ad hoc discussion of studies involving the use of the Cytosponge took place. The participants discussed that DELTA and an upcoming NHS England Pilot in secondary care would raise the awareness of the use of the Cytosponge test, as well as produce evidence that will be important for the commissioners and NICE in order to make some recommendations. However, at this stage, as both of the studies are pilot and one is in the set-up phase, it is difficult to start a campaign with the public to make them aware of the test. The participants stated that the main concern at

this stage is patients not coming forwards for the Cytosponge test and without the support of crucial information from both studies it would be difficult to progress ahead.

It was also discussed that the structure of the NHS healthcare system in the UK i.e. the division of Primary and Secondary care, is also one of the reasons for the resistance to the implementation of Cytosponge. If the system is integrated, i.e. both primary and secondary care within a hub, then there would be less friction and easy for the implementation of the Cytosponge TFF3 for the diagnostic purpose. *Note the reasons for this were not mentioned.*

## 4.2. Session 1 Breakout Rooms

The discussion in the first breakout rooms focused on implementation of the Cytosponge TFF3 as a case finding tool in primary care setting; whether there is sufficient evidence to support its use as a case finding tool for high-risk patients in primary care.

The questions given to the participants in the 1st breakout room were:

1. Is the currently available evidence on the Cytosponge-TFF3 test sufficient to implement it as a case-finding tool for high-risk patients in primary care?
2. Is there any further evidence would you like to see before the Cytosponge-TFF3 test could be implemented for case-finding in primary care?
3. What would you be looking for: Barrett's oesophagus or early oesophageal cancer?
4. How would your management of the patient be changed as a result of the Cytosponge findings?
5. Are there any specific issues you are concerned with and would like to see addressed before you would be happy to see the Cytosponge-TFF3 test implemented for patients at hight risk for oesophageal cancer in primary care?

**Participant' discussions on the above points are summarised as follows:**

1. **Cytosponge TFF3 as a risk finding tool**

One way to find people who are potentially at risk of having premalignant and malignancy of upper GI tract is by looking at their annual usage of Protease Inhibitors (PPI) or reviewing prescriptions. Methods to assess other risk factors for example alcohol use and smoking in the population could be assessed in a systematic approach to find the high-risk patients of Barrett's Oesophagus and Oesophageal cancer. If Cytosponge is systematized i.e. built into general practice, by reviewing the PPI usage and other risk factors, it could be suggested or evaluated whether a Cytosponge-TFF3 test is required or not.

A systematic review based on PPI prescription including other aspects like BMI, family history, and smoking history also allows to pick up patients at risk. If defined 'at risk' patients never had any investigation to explore the upper GI tract, they should be referred for Cytosponge TFF3 test.

Further on high-risk patients i.e. those patients with dyspepsia and reflux symptoms and weight loss are regarded as high risk and if they present with a problem the current pathway is an endoscopy referral.

Also, there are patients who have been self-medicating for years, unaware that they are at 'high risk' and equally unaware of the Cytosponge-TFF3 test available to them. They often present too late for

prevention. The current Covid-19 pandemic is making the condition worse. From this discussion we could infer that it is very important to identify this group of patients and raise awareness about the risk of self-medication as well as the Cytosponge-TFF3 test.

2. **Cytosponge TFF3 as a triage test**

Since the Cytosponge-TFF3 test is a simple, quick and easy test, it could be performed in GP surgery or in the hub and if it is implemented as triage test, it would be a game changer. There is no doubt that this test is able to detect Barrett's Oesophagus in patients, recently it has been discovered that this test has also been helpful in diagnosing dysplasia in patients who were referred for the test of Barret's oesophagus thus picking up dysplasia earlier than it would otherwise have been picked up. Lastly, the sponge is also able to pick up cells from the stomach area, that might be abnormal and indicate some other form of abnormality particularly helpful in the light of COVID and restrictions with endoscopy.

In previous trials, BEST1 and BEST2, history of reflux as well as taking PPI for certain length of time for e.g. 6 months or more, were selected as risk factors of interest for the study purposes, and were assessed both retrospectively and prospectively over a period of time.

3. **Finding of Interval Cancers**

There was not much discussion about the use of Cytosponge-TFF3 as a cancer finding tool however, some stated that after a negative GI endoscopy there are as much as 50% interval cancers could be found in the UK. The similar process of self-audit and quality control as in the upper GI endoscopy could be applied for Cytosponge-TFF3. It was also suggested that details of people undertaking the Cytosponge-TFF3 test should be recorded and subsequently passively followed up to look for the interval cancers.

## 4.3. Session 2 Breakout Rooms

The following statements/questions were put forward for the 2nd breakout room session-

0. Under what circumstances could the Cytosponge-TFF3 be used as a rule-out test for endoscopic procedure?
1. Do you have any specific concerns with using the Cytosponge-TFF3 test in this manner?
2. How could any concerns you have be addressed?
3. If it is to be used to rule-out endoscopy would that be a primary care or a secondary care decision?
4. What reassurances would you want regarding the absence of other (significant) pathologies (e.g. gastric cancer)?
5. How would you manage symptomatic patients who have a negative Cytosponge-TFF3 test?
6. How would you envisage the best use of the Cytosponge-TFF3 test to rule-out endoscopic procedures?

**Participant discussions on the above points are summarised as follows: -**

1. **Rule-in/Rule-out test**

The participants discussed that on the basis of various trial evidence the Cytosponge-TFF3 test could be used as a rule-in test and it is cost-effective in people with dyspepsia on PPI's above a certain age,

however, there currently isn't sufficient research to suggest Cytosponge-TFF3 as a rule-out test. Further multicentre research studies including patients of different ethnic groups and backgrounds who fulfil the 2 weeks wait (2WW) criteria, with ~200,000 patients may be useful to draw a conclusion. The idea would be for study participants to have their endoscopy and Cytosponge-TFF3 in parallel so that we could get a comparative safety data and diagnostics and therefore work out the sensitivity and specificity of the Cytosponge to use it as a rule-out test. In the case of symptomatic patients and dyspeptic patients it would be also helpful to have two Cytosponge-TFF3 tests to see if it was then recommended that they proceed to endoscopy, if both Cytosponge-TFF3 tests are negative and endoscopy is negative there would be reassurance that the patient is low risk.

### 2. Reason for using endoscopy and how the Cytosponge-TFF3 may replace it

At present the main reason for using endoscopy is for various concerning gastro-intestinal symptoms, primarily the suspicion of potential oesophageal cancer.

It is very important to identify the reason of requesting the endoscopy and if there is any possibility that the positive or negative Cytosponge-TFF3 would change the view about endoscopy and Cytosponge.

In UK, dyspepsia is incredibly common, about 20-30% of the population gets dyspepsia at some point in time. By combining age and other symptoms, it would be decided if the patient may need endoscopy or not; Cytosponge could be adjunct to that at that stage. Similarly, if they are referred for endoscopy because of Barrett's Oesophagus symptoms, then a positive or negative Cytosponge may be helpful in diagnosis and thus they would be less likely to get referred in case of negative Cytopsonge-TFF3 test.

In all cases, if the test is negative and the patients still have problems, they might be referred to endoscopy in the suspicion of cancer and they would undergo various other tests to find out the underlying cause.

There are not many studies regarding the Cytosponge picking up adenocarcinoma, however, the evidence in Barrett's is strong. Further steps with trials and research are needed to use Cytosponge-TFF3 as a rule-out test.

### 3. Practicalities of the roll-out of Cytosponge

The participants also discussed about the practicalities of the roll-out of Cytosponge. Since primary care is very diverse, with small GP practices being under resourced, it's just not feasible implement it in small practices. It could be done as a network in a large scale or with a gastroenterologist at the triage stage like in Cambridge. Then further prospective studies with the decision with the gastroenterologists may be helpful to rule-out endoscopy. Also, proper training is needed for the staff who is going to perform the procedures in patients.

### 4. Algorithm to use Cytosponge

Participants said that it would be helpful to have a step-by-step algorithm which will tell when it is an appropriate time would be to do a Cytosponge test and when it should be repeated potentially as well as the point where the patients are referred for endoscopy. Participants stated that they would be expecting the policy and practice in terms of the finite capacity of endoscopy and potentially if there is any possibility to reduce the use of endoscopy for low-risk patients. For this, initially some head-to-

head studies with potentially 2 week wait patients, giving Cytosponge and an endoscopy to all of them, would be helpful to work out a risk algorithm that could be applied safely to use Cytosponge at the initial stage of diagnostic procedure for at risk patients.

## 5. Plenary Session

In the plenary session, participants summarised the discussions of two breakout rooms and all the invitee participated in the discussion. The major findings of the plenary session are as follows:

There is enough evidence to support the use of the Cytosponge-TFF3 test for Barrett's and also a potential case finding for its use in low-risk populations.

There is need for further large multicentre research and data from prospective studies to think about the potential use of Cytosponge as a rule-out test as there is not enough evidence at this stage for GPs to adopt it as a rule out procedure. Such research might help us to understand which people don't require an endoscopy referral in the first instance and following a negative the Cytosponge-TFF3 test they may be safely ruled out.

There has been shift in the view about Cytosponge over the last six months, as a result of the Covid-19 pandemic. An increasing number of surgeons and GPs are interested in participating in the Delta study and are comfortable with the Barret's surveillance protocol. It has been seen as a way of supplementing fast track referrals to endoscopy and on the back of the NHS England pilot, which is identifying reflux symptoms, has resulted in a shift in the opinions of secondary care clinicians, in that that an increasing number are showing their willingness to participate in a positive way. This is very encouraging and interesting.

In terms of where the test would be done the consensus is that this isn't for every GP practice, but it could be implemented within PCN or some larger hub like community diagnostics. There was concern about how the negative and positive element of the test is going to be used. What sort of safety netting would be incorporated, or advice would be provided on the back of the negative tests? If there's maintenance of symptoms over a long period of time what would be the next type of advice or safety netting which is not as well established in single practices in a consistent way. If the test is positive, what would the next step in the system be. Where and how would that handover happen? It pitches itself into a different scenario as opposed to being done in individual practice.

It would be better if it is done within an integrated system. If it is within a hub that has both an endoscopy room and multi professional support. This support would include doctors as well as, GPs with special interest, potentially as the diagnostic team. This would allow the Cytosponge-TFF3 test to be delivered in an integrated environment that promotes its consistent use and advice and would be easy to carry on to the next stage of investigation.

## 6. Conclusions

The final conclusion or take-home message that could be drawn from this roundtable event is that the Cytosponge TFF3 could be used as a rule-in test and it is cost-effective in people with dyspepsia on PPI's above a certain age, however, there isn't enough research yet for to use it as a rule-out test.

There has been a positive shift in the view about Cytosponge over the last six months, especially during the Covid-19 pandemic as 1) most of the surgeons and GPs are interested in participating in the Delta

study and see the potential for the Cytosponge to be used as a triage tool for endoscopy referrals and 2) there seems to be an increasing confidence in the Barret's surveillance protocol.

There is a strong view that the Cytosponge-TFF3 test would be more successful if delivered within PCN or some larger hub like community diagnostics that promotes its consistent use and advice and helpful to pass on the baton to the next stage of investigation.

## 7. Recommendations

Further multicentre research studies including patients of different ethnic groups and backgrounds would be helpful to work out the sensitivity and specificity of the Cytosponge-TFF3 test to use it as a rule-out test.

## 8. References-

1. Ross-Innes CS, Debiram-Beecham I, O'Donovan M, Walker E, Varghese S, Lao-Sirieix P, et al. Evaluation of a Minimally Invasive Cell Sampling Device Coupled with Assessment of Trefoil Factor 3 Expression for Diagnosing Barrett's Esophagus: A Multi-Center Case–Control Study. PLoS Med [Internet]. 2015 Jan 1 [cited 2021 Jan 13];12(1):1–19. Available from: /pmc/articles/PMC4310596/?report=abstract
2. Fitzgerald RC, Di Pietro M, O'donovan M, Maroni R, Muldrew B, Debiram-Beecham I, et al. Cytosponge-trefoil factor 3 versus usual care to identify Barrett's oesophagus in a primary care setting: a multicentre, pragmatic, randomised controlled trial [Internet]. Vol. 396, www.thelancet.com. 2020 [cited 2021 Jan 13]. Available from: www.thelancet.com
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4. Paterson AL, Lao-Sirieix P, O'Donovan M, Debiram-Beecham I, di Pietro M, Miremadi A, et al. Range of pathologies diagnosed using a minimally invasive capsule sponge to evaluate patients with reflux symptoms. Histopathology [Internet]. 2017 Jan 1 [cited 2021 Jan 13];70(2):203–10. Available from: https://pubmed.ncbi.nlm.nih.gov/27417524/
5. Sanders ME, Schuyler PA, Simpson JF, Page DL, Dupont WD. Continued observation of the natural history of low-grade ductal carcinoma in situ reaffirms proclivity for local recurrence even after more than 30 years of follow-up. Mod Pathol [Internet]. 2015 May 5 [cited 2020 Nov 29];28(5):662–9. Available from: https://pubmed.ncbi.nlm.nih.gov/25502729/

# 9. Appendices

### 1. List of Participants

The meeting was attended by practicing GPs, academic GPs, gastroenterologists and PPI representatives. The list of total participants is as below-

- Thomas Round (KCL – GP)
- Julia Hipsley-Cox (Oxf – GP)
- Oliver Stovin (GP)
- Siobhan Campbell (PCN Nurse)
- Greg Rubin (GP)
- Mimi McCord (HCUK)
- Irene Debiram-Beecham (Principal Nurse)
- Maria O'Donovan (Pathologist)
- Alan Moss (AAH)
- Josephine Ruwende (Commissioner)
- Stephen Duffy (QMUL)
- Jodie Moffat (CRUK)
- Massimiliano Di Pietro (Gastroenterologist)
- Sean Duffy (Leeds University)
- Kathie Binysh (NHS)
- Rebecca Fitzgerald(Cam)
- Peter Saseini (KCL)
- Abigail Kerridge (Cam)
- Calvin Cheah (Cam)
- Elspeth Davies (Cam)
- Judith Offman (KCL)
- Bhagabati Ghimire (KCL)

### 2. Agenda of the meeting

**Does the Cytosponge have a role for Symptomatic Patients?**

**Roundtable Agenda – 25th February 2021**

**Time: 12:00 – 14:30**

**Chair: Peter Sasieni**

**Agenda**

| Time | Topic | Speaker |
|---|---|---|
| 12:00 – 12:10 | Opening remarks and Introduction | Peter Sasieni |
| 12:10 – 12:30 | Background of the Cytosponge and Oesophageal and Gastric pathology | Massimiliano Di Pietro |

| | | |
|---|---|---|
| 12:30 – 12:45 | How the Cytosponge could fit into Primary Care | Oliver Stovin |
| 12:45 – 12:50 | Q&A | Peter Sasieni |
| 12:50-13:15 | **BREAK** | |
| 13:15 – 13:35 | 1st Breakout session – Discussion within peer group | ALL |
| 13:35 – 13:40 | **BREAK** | ALL |
| 13:40 – 14:00 | 2nd Breakout session – Multi-disciplinary discussion | ALL |
| 14:00 – 14:25 | Feedback from breakout groups and plenary discussion | ALL |
| 14:25 – 14:30 | Closing Remarks | Peter Sasieni |

## Topics for Breakout groups:

**Session 1: Cytosponge for proactive case-finding in primary care**

Statements/Questions:

- Implementation of the Cytosponge-TFF3 test as a case-finding tool in primary care:
  - Is the currently available evidence on the Cytosponge-TFF3 test sufficient to implement it as a case-finding tool for high-risk patients in primary care?
  - Is there any further evidence would you like to see before the Cytosponge-TFF3 test could be implemented for case-finding in primary care?
  - What would you be looking for: Barrett's oesophagus or early oesophageal cancer?
  - How would your management of the patient be changed as a result of the Cytosponge findings?
  - Are there any specific issues you are concerned with and would like to see addressed before you would be happy to see the Cytosponge-TFF3 test implemented for patients at hight risk for oesophageal cancer in primary care?

**Session 2: Symptomatic referrals in primary care**

Statement/Questions:

- Under what circumstances could the Cytosponge be used as a rule-out test for endoscopic procedure?
  - Do you have any specific concerns with using the Cytosponge-TFF3 test in this manner?
  - How could any concerns you have be addressed?
  - If it is to be used to rule-out endoscopy would that be a primary care or a secondary care decision?
  - What reassurances would you want regarding the absence of other (significant) pathologies (e.g. gastric cancer)?
  - How would you manage symptomatic patients who have a negative Cytosponge test?
  - How would you envisage the best use of the Cytosponge-TFF3 test to rule-out endoscopic procedures?

## Breakout groups:

**Session 1: Cytosponge for proactive case-finding in primary care**

| Primary Care | Other |
|---|---|
| Fiona Walter (Cambridge – GP) | Mimi McCord (HCUK) |
| Joanna L Skinner (BEST 3 GP) | Irene Debiram-Beecham (Principal Nurse) |
| Thomas Round (KCL – GP) | Maria O'Donovan (Pathologist) |
| Julia Hipsley-Cox (Oxf – GP) | Alan Moss (AAH) |
| Oliver Stovin (GP) | Josephine Ruwende (Commissioner) |
| Siobhan Campbell (PCN Nurse) | Stephen Duffy (QMUL) |
| Greg Rubin (GP) | Jodie Moffat (CRUK) |
| Joanne Walsh (BEST 3 GP) | Massimiliano Di Pietro (Gastroenterologist) |
| - | Sean Duffy (Leeds University) |
| - | Kathie Binysh (NHS) |

**Session 2: Symptomatic referrals in primary care**

| Breakout group 1 | Breakout group 2 |
|---|---|
| Fiona Walter (Cambridge – GP) | Thomas Round (KCL – GP) |
| Joanna L Skinner (BEST 3 GP) | Julia Hipsley-Cox (Oxf – GP) |
| Massimiliano Di Pietro (Gastroenterologist) | Maria O'Donovan (Pathologist) |
| Mimi McCord (HCUK) | Alan Moss (AAH) |
| Irene Debiram-Beecham (Principal Nurse) | Josephine Ruwende (Commissioner) |
| Sean Duffy (Leeds University) | Stephen Duffy (QMUL) |
| Siobhan Campbell (PCN Nurse) | Jodie Moffat (CRUK) |
| Oliver Stovin (GP) | Greg Rubin (GP) |
| Kathie Binysh (NHS) | Joanne Walsh (BEST 3 GP) |