UEG Week 2015, Barcelona
Media Briefing

Advances in Personalised GI Cancer Treatment and Prevention

Tuesday October 27th 2015
Introduction:
Professor Michael Farthing
*UEG President and Vice-Chancellor of the University of Sussex, UK*

Our Speakers:
Professor Rebecca Fitzgerald FMedSci
*Professor of Cancer Prevention and Hon. Consultant Gastroenterologist Hutchison-MRC Research Centre, University of Cambridge, UK and National Institute of Health Research (NIHR) Research Professor*

Dr. Antoni Castells, MD, PhD
*Gastroenterology Department, Hospital Clinic Barcelona, Catalonia, Spain*
Reducing risk for oesophageal adenocarcinoma

Professor Rebecca Fitzgerald FMedSci
Professor of Cancer Prevention and Hon. Consultant Gastroenterologist Hutchison-MRC Research Centre, University of Cambridge, UK and National Institute of Health Research (NIHR) Research Professor
Oesophageal Cancer: Increasing incidence and Poor Outcomes

NCI SEER*Stat Database: 9 Registries released April 2013

n=2775; IUCC 2010

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Evolution of oesophageal adenocarcinoma

Squamous epithelium → Barrett’s with no dysplasia → Low-grade dysplasia (LGD) → High-grade dysplasia (HGD) → Oesophageal adenocarcinoma

- LGD: ~0.38% per year
- HGD: 1.7-12% per year
- Oesophageal adenocarcinoma: 5-13% per year
NICE approved treatments for early cancer and dysplasia in 2015

2 randomised controlled trials:
Dysplasia trial Shaheen et al NEJM 2009; LGD SURF trial JAMA 2014
Reasons for LATE diagnosis of oesophageal adenocarcinoma

- Patients and doctors wait until “alarm” symptoms
- Most patients at risk (heartburn, male, obese, family history) are not investigated
- 5-20% population reflux symptoms, 10% GP consultations for reflux

- Endoscopy is invasive and expensive
- 70% of endoscopy for heartburn and indigestion is normal
- Liam Donaldson 2008 report highlighted need to develop an alternative safe, minimally invasive, affordable test
Alternative approach: Cytosponge Technology

Cytosponge™ cell collection device

Objective biomarker assays
Cytosponge™ cell sampling
Cytosponge™ cell sampling
Barrett’s Diagnostic Biomarker

Molecular experiment to find a biomarker
Summary of data > 2,000 patients from BEST1 and BEST2 studies

• Safe
  – No serious adverse events attributed to Cytosponge

• Acceptable
  – 80% preferred Cytosponge to endoscopy (BEST1)
  – Often tolerated better than endoscopy (p=0.0003), (BEST2)

• Accuracy
  – Sensitivity 79-95% (BEST1, BEST2, CASE1 studies)
  – Specificity 92-94% (BEST1 and BEST2 studies)
Transferable Technology

27 nurses administered the Cytosponge

North Tyneside General Hospital
Newcastle: Royal Victoria Infirmary
South Tyneside NHS Foundation Trust
University Hospital of North Durham
University Hospital of North Tees
Nottingham Queen's Medical Centre
Cambridge: Addenbrookes (Bedford Hospital, Hinchingbrooke Hospital, West Suffolk Hospital)
Queen Elizabeth II Hospital
University College London
London: St Mark's Hospital
Portsmouth: Queen Alexandra
Risk stratification on Cytosponge using p53 mutation analysis

Sensitivity = 86%
Specificity = 100%

Health Economics analysis

Comparative costs:
- Advanced cancer care
- Early detection via endoscopy
- Cytosponge in primary care

Benaglia T Gastroenterology. 2013 Jan; 144:62-73
Commercial Kit

Licensed by MRC to Covidien GI Solutions (now Medtronic)
CE Marked and FDA Approval for device
Commercial launch planned for 2015 in USA
Large trial planned (n=4000) in UK primary care 2016-2019
Five Tier Strategy to Reduce Oesophageal Adenocarcinoma

Tertiary Care 150K
High risk – Treat and then monitor

Secondary Care 1.5M
Risk stratify e.g. Endoscopy + Biomarkers

Primary Care 15M
Assess whether pre-cancer (Barrett’s)
e.g. Cytosponge +/- risk stratify

Primary Care 150M
Questionnaire – determine risk factors
Education to reduce risk on individual level
Determine if investigation needed

General Population >40 yrs, 150M
Reduce exposures societal level
New proposed clinical algorithm

Screening with Cytospone™ test

- **90%** TFF3 negative test
  - Patients discharged from screening programme

- **10%** TFF3 positive test
  - Risk stratification using p53 mutation testing
    - **9%** Low risk P53 negative
      - Repeat Cytospone™ every 3-5 yrs
    - **1%** High risk P53 positive
      - Endoscopy + biopsy
      - Standard management based on clinical result
Questions?
Improving Personalised Risk Prediction is the key to Preventing Colorectal Cancer

Dr. Antoni Castells, MD, PhD.
Gastroenterology Department, Hospital Clinic, Barcelona, Catalonia, Spain
4P Medicine

Predictive
Preventive
Personalized
Participatory
The Human Genome
Molecular characterization of nucleic acids
Polyposis and non-polyposis colorectal syndromes

POLYPOSIS

Adenomas
- >100
  - CLASSICAL FAP
    - APC
    - MUTYH
    - POLE
    - POLD1
  - 20-100
    - ATENUATED FAP

Hamartomas
- PEUTZ-JEGHERS
- JUVENILE POLYPOSIS
- COWDEN SYNDROME

Serrated polyps
- SERRATED POLYPOSIS
  - >20 or >5 prox.

NON-POLYPOSIS

MMR REPAIR DEFICIENCY?
- YES
  - LYNCH SYNDROME
    - MLH1
    - MSH2
    - MSH6
    - PMS2
    - EpCAM
- No
  - FAMILIAL CRC TYPE X
  - MUTYH CRC

?
Familial adenomatous polyposis: screening

Identified mutation

Positive

Colonoscopy yearly

Polyposis

Proctocolectomy / total colectomy

• Upper endoscopy
• Abdominal CT
• Ortopantomography

Genetic testing

Negative

Exclusion
Familial adenomatous polyposis: genotype-phenotype correlation

Domains
- Armadillo repeat
- β-catenin binding (15-aa repeat)
- β-catenin downregulation (20-aa repeat)
- Microtubule binding
- EB1/RP1 binding

Exons
1 3 5 7 9 11 13 2 4 6 8 10 12 14 15

Codons
1 400 800 1200 1600 2000 2400 2800

Upper GI adenomas (1051-1600)
Attenuated FAP (5’ UTR)
Hipertrophy of the retinal pigment epithelium (542-1309)
Advanced FAP (1285, 1465)
Extracolonic manifestations (1465, 1546, 2621)

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Surgical treatment in familial adenomatous polyposis patients

- Proctocolectomy with ileoanal anastomosis
- Total colectomy with ileorectal anastomosis

• Mild familial phenotype and no rectal polyps
• Attenuated FAP

• Codon 0 - 200
• Codon >1500

• Codon 200 - 1500
• Severe familial phenotype
• Diffuse disease

• Codon 200 - 1500
Exome sequencing
Germline analysis: 25-gene, NGS panel

1260 participants
- 100% personal Hx LS-associated cancer
- 74% family Hx LS-associated cancer
- 88% fulfilled NCCN criteria for LS testing

- LS mutation: 114 patients (9.0%)
- Non-LS mutation: 71 patients (5.6%)
  - High-penetrance genes: 24 (1.9%)
  - VUS: 479 patients (38.0%)
Limitations of colonoscopy in population-based CRC screening

**Effective**
- No RCT demonstrating its efficacy
- Highest sensitivity and specificity
- Prevalence of advanced neoplasms: 10.2%\(^1\)

**Efficient**
- Huge economical effort:
  - Average-risk population (50-74 years-old) in the EU\(^2\): 146 million people
  - Costs (colonoscopy, 250 €): 3,650 M€ annually

**Harmless**
- Serious GI events (bleeding, perforation): 2.4‰\(^3\) → 35,040 patients per year

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\(^1\)Quintero & Castells, *et al.* NEJM 2012

\(^2\)EUROSTAT

\(^3\)Warren *et al.* Ann Intern Med 2009
Select those individuals who may benefit the most from colonoscopy screening

Risk stratification based on:
- Individual characteristics
- Genetic/genomic profiling
- Use of biomarkers
Risk stratification: individual characteristics

Score to estimate the likelihood of detecting advanced colorectal neoplasia at colonoscopy

- Age (p<0.001)
- Sex (p<0.001)
- Family history of CRC (p<0.001)
- Cigarette smoking (p<0.001)
- BMI (p=0.03).

Kaminski et al. Gut 2014
Human genome complexity

Copy number variants (CNV)
### 41 variants for colorectal cancer genetic susceptibility in 37 loci

- **Common, low-penetrance CRC genetic components**
- ~10% of the estimated genetic susceptibility

<table>
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</table>

Houlston et al. Nat Genet 2008
Tenesa et al. Nat Rev Genet 2009
Houlston et al. Nat Genet 2010
Tomlinson et al. PLoS Genet 2011
Kinnersley et al. Br J Cancer 2012
Fernández-Rozadilla et al. BMC Genomics 2013
Jia et al. Nat Genet. 2013
Peters et al. Gastroenterology 2013
Zhang et al. Nat Genet 2014
Whiffin et al. Hum Mol Genet 2014
Genotype – phenotype correlation of susceptibility variants in CRC patients

Abulí et al. Gastroenterology 2010
Cumulative impact of 10 common genetic variants (SNPs) on CRC risk

Dunlop et al. Gut 2012
Risk stratification: use of molecular biomarkers

- The analysis of molecular markers representing the **genetic and epigenetic alterations associated with CRC** is an attractive strategy.
- Exfoliation of neoplastic cells in the **feces** is a continuum process in patients with colorectal neoplasia.
- Tumor cells and tumor markers also enter into the **blood** in patients with colorectal neoplasia.

Summary

- Medicine will move from a reactive to a proactive discipline over the next decade—a discipline that is **predictive, personalized, preventive and participatory (P4 medicine)**.

- **Genetic testing** allow an accurate risk prediction for hereditary CRC.

- **Colonoscopy** is potentially the most effective CRC prevention strategy, but efforts should be made **to better select those individuals who may benefit the most.**

- Risk stratification based on individual characteristics, genetic/genomic profiling, and the use of biomarkers may contribute to improve CRC prevention.
Questions?