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COVER STORY

As the use of endoscopes increase, so does the risk of infections linked to endoscope reprocessing. To combat this Getinge UK provides a comprehensive range of offerings for disinfection, sterilisation and infection control.

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In moderately active ulcerative colitis:

**Plan A.**

**RETURN TO EVERYDAY LIFE**

**Efficacy**

**RELIEVE**

At 4.8g/day, 73% of patients achieve symptom improvement* and 43% of patients achieve symptom resolution as early as 2 weeks**

*Symptom improvement = decrease of at least 1 point from baseline in the respective symptom score.

**RESOLVE**

At 4.8g/day, 80% of patients achieve mucosal healing (endoscopy subscore 0 or 1) by week 6***

**RESUME**

When taken at 2.4g once daily, 4 out of 5 patients still remain in remission at 12 months****

**ASACOL 800MG MR TABLETS**

and help your patients return to everyday life.

**EFFICACY**

<table>
<thead>
<tr>
<th>2 weeks***</th>
<th>12 months****</th>
</tr>
</thead>
<tbody>
<tr>
<td>RELIEVE</td>
<td>RESOLVE</td>
</tr>
<tr>
<td>RESUME</td>
<td></td>
</tr>
</tbody>
</table>

**Combined Abbreviated Prescribing Information:**

Asacol 400mg MR Tablets, Asacol 800mg MR Tablet, Asacol 250mg and 500mg Suppositories and Asacol Foam Enema.

Presentation: Asacol 400mg MR Tablets, PL 10947/0011, each modified release tablet contains 400mg mesalamine (S-sulphasalazine) equivalent to 140mg mesalazine (mesalamine). Bottles of 120, £12.04. Asacol 800mg MR Tablets, PL 10947/0012, each modified release tablet contains 800mg mesalamine (S-sulphasalazine) equivalent to 280mg mesalazine. Bottles of 160, £17.71.

Asacol 250mg Suppositories, PL 10947/0013, each containing 250mg mesalamine. Pack of 10, £2.82. Asacol Foam Enema, PL 10947/0014, 1g mesalamine per metered dose. Canister containing up to 14 metered doses, 14 disposable applicators and 14 disposable plastic bags, £2.72.


Dosage and administration: ADULTS: 400mg Tablets: Acute disease: 6 tablets a day in divided doses, with concurrent corticosteroidal therapy when clinically indicated. Maintenance therapy: 3 to 4 tablets a day, once daily or divided doses. 400mg Tablets: Mild acute exacerbations of ulcerative colitis: 3 tablets a day in divided doses. Moderate acute exacerbations of ulcerative colitis: 3 to 4 tablets a day in divided doses. Maintenance of remission of ulcerative colitis: Up to 3 tablets a day, once daily or in divided doses. Maintenance of remission of Crohn’s colitis: Up to 3 tablets a day in divided doses. Suppositories: 250mg 1 to 3 tablets a day, in divided doses, with the last dose at bedtime. 500mg: A maximum of 3 a day, in divided doses, with the last dose at bedtime. Foam Enema: A maximum of 200mg (6 to 12 tablets) in divided doses as an single daily dose for 4 weeks. ELDERLY: The normal adult dosage may be used unless renal function is impaired. CHILDREN: 300mg Tablets Not recommended. 400mg Tablets, Suppositories, Foam Enema Not for neonates and infants.

**Contra-indications:** A history of sensitivity to salicylates or renal sensitivity to salicylates. Confirmed severe renal impairment (creatinine clearance < 30mL/min). 400mg Tablets, Suppositories and Foam Enema only: Children under 2 years of age. 800mg Tablets only: Hypersensitivity to any of the ingredients. Severe hepatic impairment. Gastric or duodenal ulcer, haemorrhagic tendency.

**Precautions:** Use in the elderly should be cautious and subject to patients having a normal renal function. Asacol should be used with extreme caution in patients with confirmed mild to moderate renal disease, or patients with impaired hepatic or renal function or patients with active upper gastrointestinal disease. No dosage recommendation.

CHILDREN: 800mg Tablets: No dosage recommendation.

ELDERLY: 250mg Tablets: A maximum of 3 a day, in divided doses, with the last dose at bedtime.

Foam Enema: A maximum of 3 a day, in divided doses, with the last dose at bedtime.

**Etiology:**

**In moderately active ulcerative colitis:**

**800mg Tablets:**

- 400mg Tablets and 800mg Tablets only: Foam Enema for distal colon disease only.
- Maintenance of remission. Suppositories particularly appropriate for distal disease, Foam Enema for distal colon disease only.
- Combination of 200mg and 100mg (2 tablets) in divided doses for 4-6 weeks.

**400mg Tablets, Suppositories, Foam Enema:**

- Doses as single daily dose for 4-6 weeks.
- Enema:
  - No dosage recommendation.
  - 400mg Tablets, Suppositories, Foam Enema:
  - A maximum of 3 a day, in divided doses, with the last dose at bedtime.

**500mg:**

**CHILDREN: 800mg Tablets:**

- No dosage recommendation.

**ASACOL 250mg Suppositories:**

- **Asacol 500mg Suppositories**
  - PL 10947/0013, each containing 250mg mesalazine. Packs of 10, £4.82.
  - PL 10947/0014, each containing 500mg mesalazine. Packs of 10, £4.82.
  - PL 10947/0011; each modified release tablet contains 500mg mesalazine. Packs of 10, £29.41.

**Presentation:**

- Suppositories and Asacol Foam Enema: Combined Abbreviated Prescribing Information:
  - 1 (disease of rectosigmoid region) or 2 (disease of descending colon) metered dose inhalers.
  - Adverse events should also be reported to Warner Chilcott UK Ltd on 0800 0328701 for eligible patients prescribed Asacol.
  - Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard

**Support programme for eligible patients prescribed Asacol.**

**Adverse events** should be reported.

**ASACOL 800MG MR TABLETS**

Relieve, resolve, resume

**Legal category:** POM.

**Marketing Authorisation Holder:** Warner Chilcott UK Ltd, Old Belfast Road, Millbrook, Larne, County Antrim, BT40 2SH, UK. Asacol is a trademark. Refer to Summary of Product Characteristics before prescribing.

**Date of preparation:** March 2014. Job Bag Number: UK/04/0005/04-11(3)

**References:**

6. References:

**www.assuresupport.co.uk**

Support programme for eligible patients prescribed Asacol.
Biological Revolution

The last few months has seen dramatic changes with regards drug therapies for inflammatory bowel disease. In a short space of time we are seeing the arrival of a new 1st in class product, the introduction of generic biological agents and an extension to the indication for use of agents previously reasonably restricted for Crohn’s only being more widely utilised in ulcerative colitis.

Now more than ever our patients need equality of access to these therapies. Now more than ever we need to see the N in NICE and NHS in action. The National Institute for Health and Care Excellence provides national advice and guidance to improve health (and social) care. Clinical commissioning groups (CCGs) are NHS organisations, set up by the Health and Social Care Act 2012, to organise the delivery of services in England.

On the face of things CCGs should facilitate the implementation of NICE guidelines. The definition of facilitate is “to make an action easy or easier”. I am not sure how many gastroenterologists would describe their local CCGs as facilitators.

Anecdotally CCGs delay implementation of NICE guidelines for as long as possible and largely for non-clinical reasons. Nationally CCGs seem to have widely differing levels of interaction with the Trusts they work with. This can lead to a proliferation of locally agreed pathways and protocols which seem to re-invent and potentially water down national guidelines.

With the availability of cheaper generics a potential for shared reduction in costs “gain-share” has been proposed. Visionary CCGs and Trusts have split the cost savings enabling Trusts to re-invest in the IBD service - which will need more support to deliver the increasingly complicated drug regimens available. There is, however, a risk that these savings will be used to balance books as more Trusts struggle financially. Without this investment the implementation of National guidelines may be impacted and this will not lead to equality of access for our patients.

Dr A Poullis
St George’s Hospital
London
Optimisation with Salofalk Granules for patients inadequately maintained on previous mesalazine resulted in:

- 47% less routine hospital visits
- 60% less hospital visits due to flare-up
- 44% less GP visits due to UC flare-up
- 50% less steroid courses used

"An oral ulcerative colitis treatment that’s a step change, not a step up
Now that’s progress"

When mesalazine doesn’t seem to be working, stepping up to immunosuppressants might not be the only option.

For those patients who could benefit from a simpler routine Salofalk Granules come in a convenient little sachet, only need to be taken once a day and even have a tasty vanilla flavour.

Oh and if the inflammation is in the distal colon, the granules are pretty good at getting there too.

Salofalk® Granules
Mesalazine, the Dr Falk way

Prescribing Information (Please refer to full SPC before prescribing):
Salofalk gastro-resistant prolonged-release granules

Presentation: Stick-formed or round, greyish white gastro-resistant prolonged-release granules in sachets containing 500mg, 1000mg, 1.5g or 3g mesalazine per sachet.

Indications: Treatment of acute episodes and the maintenance of remission of ulcerative colitis.

Dosage: Adults: Once daily 1 sachet of 3g granules, 1 or 2 sachets of 1.5g granules or 3 sachets of 1000mg or 500mg granules (equivalent to 1.5 – 3.0g mesalazine daily) preferably to be taken in the morning, according to the individual clinical requirement. It is also possible to take the prescribed daily dose in three divided doses (1 sachet of 500mg granules three times daily or 1 sachet of 1000mg granules three times daily) if this is more convenient.

Maintenance: 0.5g mesalazine three times daily (in the morning, at midday and in the evening) corresponding to a total dose of 1.5g mesalazine per day. For patients known to be at increased risk for relapse for medical reasons or due to difficulties to adhere to application of three daily doses the dosing schedule can be adapted to 3.0g mesalazine given as a single daily dose, preferably in the morning. Children: There is only limited documentation for an effect in children (age <18 years). Children 6 years of age and older: Active disease: To be determined individually, starting with 10-30mg/kg/day once daily preferably in the morning or in divided doses. Maximum dose: 75mg/kg/day. The total dose should not exceed the maximum adult dose. Maintenance treatment: To be determined individually, starting with 15-30mg/kg/day in divided doses. The total dose should not exceed the recommended adult dose. It is generally recommended that half the adult dose may be given to children up to a body weight of 40kg, and the normal adult dose to those above 40kg.

Method of administration: The granules should be taken on the tongue and swallowed, without chewing, with plenty of liquid.

Contra-indications: Hypersensitivity to salicylates or any of the excipients. Severe impairment of renal function or if the patient is known to be at increased risk for relapse for medical reasons or due to difficulties to adhere to application of three daily doses.

Method of administration: The granules should be taken on the tongue and swallowed, without chewing, with plenty of liquid. Contra-indications: Hypersensitivity to salicylates or any of the excipients.

Warnings/Precautions: Blood tests (differential blood count, liver function parameters such as ALT or AST, serum creatinine) and urinary status (slop tests) should be determined prior to and during treatment at the discretion of the treating physician. Caution is recommended in patients with impaired hepatic function.

Adverse effects: Headache, dizziness, allergic and/or anaphylactic reactions, flushing, rash, urticaria, prickly heat, angioedema, hypoglycaemia, hyperglycaemia, pancreatitis, impaired renal function including acute and chronic interstitial nephritis and renal insufficiency, apnoea, myalgia, arthralgia, hyperosmolarity reactions such as allergic anaphylaxis, drug fever, lupus erythematosus syndrome, pancreatitis, changes in hepatic function parameters, hepatitis, cholestatic hepatitis and oligaemia per os.

Further information is available on request.

References:

Date of preparation: March 2013

Further information is available on request.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard (UK residents) or at http://www.hpra.ie/EN/Safety-Quality/Online-forms.aspx (residents of the Republic of Ireland). Adverse events should also be reported to Dr Falk Pharma UK Ltd.
PROSPECTIVE COMPREHENSIVE GENOMIC PROFILING OF ADVANCED GASTRIC CARCINOMA CASES REVEALS FREQUENT CLINICALLY RELEVANT GENOMIC ALTERATIONS AND NEW ROUTES FOR TARGETED THERAPIES


*Foundation Medicine Inc., Cambridge, Massachusetts, USA; †Chao Family Comprehensive Cancer Center, Division of Hematology-Oncology, Department of Medicine, University of California Irvine School of Medicine, Orange, California, USA; ‡Dana–Farber Cancer Institute, Boston, Massachusetts, USA; §University of Chicago, Chicago, Illinois, USA; ¶Comprehensive Cancer Centers of Nevada, Las Vegas, Nevada, USA; ¶Department of Pathology and Laboratory Medicine, Albany Medical College, Albany, New York, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

KeyWords. Gastric cancer • Sequencing • Targeted therapy • Mutation • Profiling • MET

Abstract

Background. Gastric cancer (GC) is a major global cancer burden and the second most common cause of global cancer-related deaths. The addition of anti-ERBB2 (HER2) targeted therapy to chemotherapy improves survival for ERBB2-amplified advanced GC patients; however, the majority of GC patients do not harbor this alteration and thus cannot benefit from targeted therapy under current practice paradigms.

Materials and Methods. Prospective comprehensive genomic profiling of 116 predominantly locally advanced or metastatic (90.0%) gastric cancer cases was performed to identify genomic alterations (GAs) associated with a potential response to targeted therapies approved by the U.S. Food and Drug Administration or targeted therapy-based clinical trials.

Results. Overall, 78% of GC cases harbored one clinically relevant GA or more, with the most frequent alterations being found in TP53 (50%), ARID1A (24%), KRAS (16%), CDH1 (15%), CDKN2A (14%), CCND1 (9.5%), ERBB2 (8.5%), PIK3CA (8.6%), MLL2 (6.9%), FGFR2 (6.0%), and MET (6.0%). Receptor tyrosine kinase gastric cancer alterations were detected in 20.6% of cases, mainly ERBB2, FGFR2, and MET amplification, with ERBB2 alterations evenly split between amplifications and base substitutions. Rare BRAF mutations (2.6%) were also observed. One MET-amplified GC patient responded for 5 months to crizotinib, a multitargeted ALK/ROS1/MET inhibitor.

Conclusion. Comprehensive genomic profiling of GC identifies clinically relevant GAs that suggest benefit from targeted therapy including MET-amplified GC and ERBB2 base substitutions.

The Oncologist 2015;20:1–9

Implications for Practice

Despite description of many potentially clinically relevant genomic alterations in retrospective research studies, these alterations are not regularly assessed in a comprehensive manner in clinical practice. This study demonstrates the feasibility of prospective comprehensive genomic profiling (CGP) for advanced gastric carcinoma. We demonstrated a high frequency of genomic alterations associated with potential benefit from targeted therapies. CGP in this setting may inform therapeutic options beyond standard of care testing by identifying genomic alterations such as point mutations in the kinase domain of ERBB2 and MET amplification. Genotype-directed management is highlighted by the response of a MET-amplified gastric carcinoma patient to crizotinib.

Introduction

Gastric cancer (GC) is the second most frequent cause of cancer-related death worldwide [1]. The majority of patients present with advanced disease, and the overall 5-year survival rate is <28%, compared with <5% for patients presenting with metastatic disease [2–4]. The clinical heterogeneity of GC is highlighted by significant worldwide geographic variations, differences in anatomic origin (proximal vs. distal), risk factors including Helicobacter pylori infection and dietary patterns, and a poorly understood relationship to Asian ethnicity [5–7]. Within the common intestinal histologic subtype, there are differences in ERBB2 amplification frequencies (proximal vs. distal) and association with H. pylori and progression from a metaplastic background (distal vs. proximal, intestinal type) [8–10].

Correspondence: Siraj M. Ali, M.D., Ph.D., Foundation Medicine, Inc., 150 Second Street, Cambridge, Massachusetts, 02141, USA. Telephone: 617-418-2241; E-Mail: Siraj@Foundationmedicine.com Received September 24, 2014; accepted for publication February 4, 2015. ©AlphaMed Press 2015-140378
Efforts to identify predictive biomarkers to guide decision making for systemic therapy have yielded inconsistent results. To date, the only validated predictive biomarker for targeted therapy is ERBB2 amplification, which predicts benefit from the anti-ERBB2 (HER2) antibody trastuzumab in advanced disease [8, 11, 12].

Systemic therapy for metastatic, relapsed, or refractory GC is largely based on empiric 5-fluorouracil and platinum combinations, and there are no definitive clinical predictors of response [13]. Although trastuzumab offers improved survival for the 7%–34% of GC patients with ERBB2 amplification, there are no approved molecularly directed therapies for the majority of patients [8, 14]. Although the recent approval of the anti-VEGFR2 antibody ramucirumab increases the GC armamentarium, there are no validated predictive biomarkers to identify patients who may derive benefit from anti-VEGFR targeted therapies [13, 15].

Large-scale retrospective whole-genome sequencing analyses have highlighted recurrent genomic alterations in gastric cancer such as ARID1A, CDH1, RHOA, and FGFR2 [10, 16–18]. Prospective comprehensive genomic profiling based on a clinical next-generation sequencing (NGS) assay in the course of clinical care can identify novel and known clinically relevant genomic alterations (GAs) and increase understanding of the underlying biology and immediately inform patient management options. In this study, we present a large series of primarily relapsed and metastatic gastric carcinoma clinical specimens that underwent prospective comprehensive genomic profiling and highlight therapeutic implications.

Materials and Methods

Comprehensive genomic profiling using a clinical NGS-based assay (FoundationOne) was performed in a Clinical Laboratory Improvements Amendment-certified, College of American Pathologists-accredited laboratory (Foundation Medicine, Cambridge, MA, http://www.foundationmedicine.com) using validated methods [19]. Clinical samples were sent in from both academic and community oncologists for genomic profiling in the context of clinical care, and patient outcomes in selected cases were obtained from the primary treating physician. With the exception of three samples received as extracted DNA, a pathologist reviewed hematoxylin and eosin-stained slides to confirm diagnosis of GC and to ensure adequate formalin-fixed, paraffin embedded (FFPE) review. The two-tailed Fisher’s exact test was used to determine statistical significance of all group comparisons. Local site permissions were used to study these samples.

DNA was extracted from unstained FFPE specimens using the Promega Maxwell 16 Tissue LEV DNA kit (Promega, Madison, WI, http://www.promega.com) and quantified using an Invitrogen PicoGreen fluorescence assay (Thermo Fisher Scientific, Waltham, MA, http://www.thermofisher.com). Library construction was performed with 50–200 ng of DNA sheared by sonication (E210; Covaris, Woburn, MA, http://covarisinc.com) to ~100–400 base pairs before end repair, dA addition, and ligation of indexed Illumina sequencing adaptors (Illumina, San Diego, CA, http://www.illumina.com). Prior to hybrid selection and sequencing, libraries were amplified with polymerase chain reaction (PCR) for 10 cycles using KAPA HiFi (Kapa Biosystems, Wilmington, MA, http://www.kapabiosystems.com). Solution-based hybrid selection was performed with a custom bait set of 120-bp biotinylated DNA oligonucleotides (Integrated DNA Technology, Coralville, IA, http://www.idtdna.com) covering 3,769 exons of 236 cancer-related genes and 47 introns of 19 genes frequently rearranged in cancer. The Illumina HiSeq 2500 and Illumina HiSeq 2500 platforms were used to perform 49 × 49 paired-end sequencing. Sequence alignment, PCR duplicate-read removal, and local alignment optimization were performed using Burrows-Wheeler aligner bwa-0.5.9 (SourceForge; Slashdot Media, San Francisco, CA, http://slashdotmedia.com), Picard 1.47 (Broad Institute, Cambridge, MA, http://broadinstitute.github.io/picard/), SAM Tools samtools-0.1.12a (SourceForge; Slashdot Media), and GATK 1.0.4705 (Broad Institute).

Variant calling was performed using custom tools. Base substitutions were called using a Bayesian methodology, and short insertions-deletions (indels) were called using local assembly. Somatic variants were annotated using COSMIC, and germline variants were removed using dbSNP. Rearrangements were called using chimeric read pairs clustered by genomic position. Copy number alterations (CNAs) were detected by fitting a statistical copy-number model to normalized coverage and allele frequencies at all exons and ~3,500 genomewide single nucleotide polymorphisms and accounting for stromal admixture. An extensive validation was performed for base substitutions, short indels, and CNAs. To validate CNA detection, seven tumor cell lines bearing 19 focal gene amplifications (6–15 copies, 15 genes) and 9 homozygous gene deletions (6 genes) with their matched normal cell lines (thereby maintaining consistent genotypes) were pooled to create five ratios ranging from low to high tumor content (20%–75%), creating a total test set of 210 CNAs.

High performance was achieved for both high-level amplifications (copy number ≥8) and homozygous deletions when tumor purity was as low as 30%; sensitivity was 99% (91 of 92) with positive predictive value >99% (127 of 127). Performance was reduced for lower CNAs (6–7 copies) and at lower sample purities (20%–30%), with overall sensitivity >80%. Cancer-related alterations were defined as those that are known sites of somatic mutation, truncations or homozygous deletions of known tumor suppressor genes, and amplifications of oncogenes and fusions of genes known to be rearranged in solid tumors.

Clinically relevant GAs were defined as those that suggested potential response to targeted therapies approved in gastric carcinoma or in other tumor types or that suggested benefit from targeted therapy under development and being administered in the context of a clinical trial. The two-tailed Fisher’s exact test was used to determine statistical significance of all group comparisons. Local site permissions were used to study these samples.

Results

Comprehensive genomic profiling was performed on 116 GC cases. The median patient age at time of testing was 62 years (range: 26–87 years) (Table 1). Sixty-five (56%) specimens were from male patients. The stage distribution is shown in Table 1. Of the samples, 69% (n = 80) were from the primary GC and 31% (n = 36) were from metastatic sites including ovary (n = 7), peritoneum (n = 4), omentum (n = 3), colon (n = 3), bone (n = 3), pleural fluid (n = 3), lymph node (n = 3), ascites (n = 2), esophagus (n = 2), small intestine (n = 2), mesentery (n = 1), liver (n = 1), pelvis (n = 1), and soft tissue (n = 1).
Overall, 501 cancer-related genomic alterations were identified in 116 cases, yielding an average of 4.32 alterations per sample (Table 1; Fig. 1). Of 501 GAs identified, 210 (41%) were clinically relevant alterations, yielding an average of 1.8 clinically relevant GAs per case (Table 1). Moreover, 78% of GC cases harbored at least 1 clinically relevant variant associated with targeted therapies approved by the U.S. Food and Drug Administration (FDA) or mechanism-based trials (Table 2). The most common clinically relevant GAs were KRAS, CDKN2A, CCND1, ERBB2, PIK3CA, MLL2, MET, PTEN, ATM, DNMT3A, NF1, NRAS, and MDM2 (Table 2). The most common GAs in the 116 cases were TP53 (58 cases, 50%), ARID1A (28 cases, 24%), and CDH1 (17 cases, 15%).

Twenty-eight cases (24%) harbored loss-of-function ARID1A alterations (Fig. 2). ARID1A-altered samples harbored an increased frequency of CREBBP variants (p < .0005), PIK3CA variants (p = .0017), and MLL2 variants (p = .019) and were less likely to harbor TP53 variants (p < .050). In this series, tumors with ARID1A alterations had less frequent amplifications of cancer-related genes compared with cases with wildtype ARID1A. This finding was statistically significant but was not replicated in an independent set of 192 gastric carcinomas (data not shown). All other ARID1A findings remained significant with a type I error rate of < .05 with a multiple hypothesis correction applied.

Somatic CDH1 mutations were found in 6 of 24 (25%) diffuse GC cases compared with 11 of 92 (12%) nondiffuse GC cases (p = .12). Matched normal tissue was not available to investigate germline CDH1 status. Enrichment of APC, CREBBP, and MLL2 alterations was observed in intestinal GC; 3 of 12 cases (25%) contained APC mutations compared with 3 of 104 cases (2.9%) of nonintestinal GC (p = .014). APC variants were not observed in any of the 24 diffuse GC cases. CREBBP was altered in 4 of 12 (33%) intestinal cases compared with 2 of 104 (1.9%) nonintestinal cases (p < .001), and MLL2 was altered in 4 of 12 (33%) intestinal cases compared with 4 of 104 (3.8%) nonintestinal cases (p = .0038).

Alterations of genes involved in mismatch repair were observed in this series at a frequency of 2.6% for MLH1, 0.8% for MSH2, and 0.8% for MSH6. Three of these five cases harbored truncating alterations that are predicted to cause loss of function, and no single case contained more than one alteration in this pathway. No information on microsatellite stability assessed by PCR testing was available.

Alterations in receptor tyrosine kinases (RTKs) were harbored by 24 cases (20.6%). Ten samples (8.6%) harbored ERBB2 alterations, 5 contained somatic base substitutions and 5 harbored amplifications (6–24 copies), with these events being mutually exclusive. ERBB2 base substitutions in this series consisted of R678Q (two cases), S310F (one case), L755S (one case), and V842I (one case). One case harbored both ERBB2 R678Q and MET amplification. CDH1 alteration was not associated with ERBB2 alteration in our GC sample (data not shown).

Seven cases (6%) harbored MET amplifications (7–30 copies) and seven cases (6%) had FGFFR2 amplifications (12–32 copies) (Table 2). One patient with MET-amplified gastric carcinoma received crizotinib and achieved disease control (Fig. 3).

One FGFFR2-altered case also harbored a coexisting ARID1A alteration. EGFR alterations were detected in four cases (3.4%) consisting of two amplifications, one point mutation (F795V), and one case with a deletion of exons 2–7 (EGFR viii). Rare RTK alterations identified included FLT3 (amplification; one case), KIT (D716N; one case), and FGFFR3 (amplification; one case) (supplemental online Table 1). EGFR amplifications were not exclusive of other RTK alterations because they coexisted with FGFFR2 amplification (one case) and both MET and ERBB2 amplifications (one case). No ROST1 alterations, including fusions, were detected. Among clinically relevant alterations in other kinases, BRAF alterations occurred at a frequency of 2.6%, two cases harbored D594X and one case harbored G469V (supplemental online Table 1). Alterations in vascular endothelial growth factor receptors 1–3 (VEGFR1–3) were limited to KDR (VEGFR2) R275* and FLT4 (VEGFR3) S637R in all 116 GC cases, and neither alteration has been linked to benefit from ramucirumab [13, 15].

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**Table 1.** Clinicopathological and genomic characteristics of 116 gastric cancer cases prospectively assayed by a comprehensive genomic profiling assay

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age, average, years</td>
<td>59.5</td>
</tr>
<tr>
<td>Sex, %</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44</td>
</tr>
<tr>
<td>Female</td>
<td>56</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Diffuse type</td>
<td>24 (20.7)</td>
</tr>
<tr>
<td>Intestinal type</td>
<td>12 (10.3)</td>
</tr>
<tr>
<td>Gastric carcinoma NOS</td>
<td>80 (69.0)</td>
</tr>
<tr>
<td>Histologic grade, n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>2</td>
<td>24 (20.7)</td>
</tr>
<tr>
<td>3</td>
<td>90 (77.6)</td>
</tr>
<tr>
<td>Stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>II</td>
<td>7 (6.0)</td>
</tr>
<tr>
<td>III</td>
<td>21 (18.1)</td>
</tr>
<tr>
<td>IV</td>
<td>84 (72.4)</td>
</tr>
<tr>
<td>Site of tumor, n (%)</td>
<td></td>
</tr>
<tr>
<td>Primary site</td>
<td>80 (69)</td>
</tr>
<tr>
<td>Metastatic sites*</td>
<td>36 (31)</td>
</tr>
<tr>
<td>GA</td>
<td></td>
</tr>
<tr>
<td>Total alterations</td>
<td>501</td>
</tr>
<tr>
<td>Average per sample</td>
<td>4.3</td>
</tr>
<tr>
<td>Clinically relevant GA</td>
<td>201</td>
</tr>
<tr>
<td>Clinically relevant GA per sample</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*Including ovary (n = 7), peritoneum (n = 4), omentum (n = 3), colon (n = 3), bone (n = 3), pleural fluid (n = 3), lymph node (n = 3), ascites (n = 2), esophagus (n = 2), small intestine (n = 2), mesentery (n = 1), liver (n = 1), pelvis (n = 1), and soft tissue (n = 1).

Abbreviations: GA, genomic alteration; NOS, not otherwise specified.
The phase III ToGA trial demonstrated the power of molecular testing to prospectively identify a molecularly defined subgroup of patients who are likely to benefit from anti-ERBB2 (HER2)-directed therapy, the addition of trastuzumab to standard 5-fluorouracil/platinum chemotherapy led to a statistically significant 2.5-month improvement in overall survival for ERBB2-amplified gastric cancer [8]. The methods of molecular testing, however, are also important, as demonstrated by the negative results of the TyTAN trial. In that trial, the addition of lapatinib (an oral HER2 inhibitor) to paclitaxel did not lead to significant improvement in progression-free survival or overall survival (OS) when compared with single-agent paclitaxel as second-line treatment in ERBB2-amplified GC, as determined by fluorescence in situ hybridization (FISH) alone [20]. Subgroup analysis indicated that ERBB2 amplification and immunohistochemistry (IHC) 3+ derived a significant 6.4-month improvement in overall survival. Similarly, early reporting from the LoGIC trial demonstrated OS improvements in Asian patients and those aged <60 years but failed to demonstrate an association between OS and IHC score [21]. Neither of these trials included patients with ERBB2 mutations.

Prior reports characterizing the genomic landscape of gastric carcinoma have relied on banked, therapy-naive tissue from primary resections [10, 16–18, 25, 26]. Recent work from the Cancer Genome Atlas has defined four groups of gastric carcinomas, each harboring positivity for Epstein-Barr virus (EBV), microsatellite instability, or multiple copy number amplifications while genomically stable or characterized by chromosomal instability [27]. Characteristic single-gene alterations were often but not perfectly associated with each group; EBV-positive gastric carcinomas often harbored PIK3CA alterations, and the genomically stable group often harbored RHOA alterations [27]. These groups offer insight into common etiologies but do not currently direct therapeutic decision making.

In contrast, the prospective series presented in this study reflects samples characteristic of clinical practice because the series is composed of cases from patients typically with advanced gastric carcinoma. A high percentage of cases (78%) harbor clinically relevant genomic alterations, including 1 in 5 cases (20.6%) with alterations in RTKs, suggesting the utility of comprehensive genomic profiling to match patients with targeted therapies of specific potential benefit in clinical trials (Table 2). For the common genomic alterations KRAS, ARID1A, and TP53, their clinical relevance is best linked to possible benefit from clinical trials with targeted agents. The recent FDA approval of trametinib as a MEK pathway inhibitor for melanoma has resulted in the anecdotal use of trametinib in other tumors types and assessment in clinical trials for other indications [28].

Figure 1. Tile plot of genomic alterations in 116 consecutive gastric cancer cases.
Both amplifications and base substitutions were observed in carcinoma patient has responded to anti-ERBB2 (HER2)-targeted therapy alterations may also be oncogenic drivers in GC, and at least one such breast carcinoma patient cannot be detected by IHC or FISH [29].

We identified five GC cases with ERBB2-activating base substitutions, which cannot be detected by IHC or FISH [29].

Similarly for TP53 and ARID1A, targeted therapies are in clinical development, such kevetrin (NCT01664000), and inhibitors of chromatin remodeling. A recent development is the paradigm of master trials, such as the Novartis Signature Trial, with multiple agents and genomically defined entry criteria for advanced cancers rather than restriction to a tumor type. Such a trial design can accommodate the addition of future therapies to be developed, and genomic profiling can provide the rationale for entering patients.

We identified five GC cases with ERBB2-activating base substitutions, which cannot be detected by IHC or FISH [29].

The recent description of somatic ERBB2 base substitutions in breast carcinoma and micropapillary urothelial carcinoma suggests that such alterations may also be oncogenic drivers in GC, and at least one such breast carcinoma patient has responded to anti-ERBB2 (HER2)-targeted therapy [29–32]. Both ERBB2 amplifications and base substitutions were observed in our patient series but were mutually exclusive, consistent with observations in breast carcinoma [33]. The low frequency in this series (4.3%) of ERBB2 amplification in contrast with the 20% frequency observed in previous studies is likely due to a selection bias, that is, cases submitted for genomic profiling were previously tested for ERBB2 amplification and were negative for ERBB2, prompting a search for therapeutic alternatives [34].

Among ERBB2 base substitutions in this series, some have been functionally characterized as activating and sensitive to lapatinib (S310F, V842I) or resistant to lapatinib (L755S) [30]. The frequency of 4.3% was very similar to the frequency reported in other series, confirming that no selection bias was present because standard of care testing does not detect these clinically relevant alterations [34, 35]. Although ERBB2 R678Q was not found to be activating or to confer resistance to anti-ERBB2 (HER2)-targeted therapy, it has been observed multiple times in the context of cancer, which may indicate biologic significance.

### Table 2. Therapeutic implications of recurrent somatic genomic alterations in 116 clinical gastric cancer cases analyzed by prospective genomic profiling

<table>
<thead>
<tr>
<th>Gene</th>
<th>Type of alteration</th>
<th>Frequency (%)</th>
<th>Approved anticancer drugs</th>
<th>Novel targeted therapies under clinical investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>Sub/indel</td>
<td>50</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>ARID1A</td>
<td>Sub/indel</td>
<td>24</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>KRAS</td>
<td>Sub</td>
<td>16</td>
<td>None</td>
<td>trametinib</td>
</tr>
<tr>
<td>CDH1</td>
<td>Sub/indel</td>
<td>15</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Sub/indel</td>
<td>14</td>
<td>None</td>
<td>LEE011</td>
</tr>
<tr>
<td>CCND1</td>
<td>Amp</td>
<td>9.5</td>
<td>None</td>
<td>LEE011, palbociclib</td>
</tr>
<tr>
<td>ERBB2</td>
<td>Amp, sub</td>
<td>8.6</td>
<td>Pertuzumab, trastuzumab, laptatanib</td>
<td>Afatinib, neratinib</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Amp, sub</td>
<td>8.6</td>
<td>Everolimus, temsirolimus</td>
<td>BYL719, BKM120,</td>
</tr>
<tr>
<td>MLL2</td>
<td>Sub</td>
<td>6.9</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>FGFR2</td>
<td>Amp</td>
<td>6.0</td>
<td>Pazopanib, ponatinib</td>
<td>Dovitinib, AZD4547</td>
</tr>
<tr>
<td>MET</td>
<td>Amp</td>
<td>6.0</td>
<td>Crizotinib, cabozantinib</td>
<td>Rilotumumab, AMG337</td>
</tr>
<tr>
<td>PTEN</td>
<td>Sub/indel</td>
<td>5.2</td>
<td>Everolimus, temsirolimus</td>
<td>None</td>
</tr>
<tr>
<td>ATM</td>
<td>Sub</td>
<td>4.3</td>
<td>None</td>
<td>Olaparib</td>
</tr>
<tr>
<td>DNM13A</td>
<td>Sub</td>
<td>4.3</td>
<td>None</td>
<td>Decitabine, 5-azacitidine</td>
</tr>
<tr>
<td>NF1</td>
<td>Sub/indel</td>
<td>4.3</td>
<td>None</td>
<td>Trametinib, everolimus, temsirolimus</td>
</tr>
<tr>
<td>NRAS</td>
<td>Sub</td>
<td>4.3</td>
<td>None</td>
<td>Trametinib</td>
</tr>
<tr>
<td>MDM2</td>
<td>Amp</td>
<td>4.3</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>BRAF</td>
<td>Mut</td>
<td>2.5</td>
<td>Vemurafenib; dabrafenib or trametinib</td>
<td>MEK162, LGX818</td>
</tr>
</tbody>
</table>

Only representative examples of investigational compounds are shown because of space constraints. Abbreviations: Amp, amplifications; Indel, small insertions and/or deletions; Sub, base substitutions.

**Figure 2.** Lollipop plot graphically depicting the location of ARID1A genomic alterations in the 28 ARID1A-altered gastric cancer cases (one arrowhead per genomic alteration [GA] in this series, with some cases harboring several ARID1A GAs).
Activating ERBB2 base substitutions appear to be sensitive to neratinib, suggesting a possible pathway to clinical treatment, and genomically selected basket trials of neratinib (NCT01953926) are ongoing for ERBB2-altered tumors [30].

Previous studies have strongly associated ERBB2-amplified gastric carcinomas with intestinal type histology and proximal gastric location [8, 12]. All five ERBB2-amplified GC cases in this series had histology diagnosed as or at least suggestive of the intestinal subtype but were approximately evenly distributed in site of origin between the proximal and distal stomach (supplemental online Table 1). In contrast, ERBB2 base substitutions were associated with signet ring features in three of four cases with histology available for review. The differing histology of these cases may suggest differing clinicopathologic characteristics of ERBB2-amplified GC compared with ERBB2 base-substituted gastric carcinomas, but this awaits independent confirmation in a larger series.

Alterations in the FGFR family are well recognized as oncogenic drivers [36, 37]. FGFR2 was amplified at 6% in this GC series, similar to a previous study [18, 38]. Limited clinical studies have shown that FGFR2-amplified breast carcinoma patients responded favorably to dovitinib, a multikinase inhibitor that inhibits FGFR family members [39]. For FGFR2-amplified GC, preclinical evidence suggests such tumors are sensitive to FGFR targeted therapy, and molecularly stratified clinical trials are ongoing (NCT01719549) [40].

Amplification of MET is a known driver of gastroesophageal and lung carcinomas and other tumor types [38, 41, 42]. We identified MET amplification (>6 copies) in 6% of GC cases in this series. Based on the genomic profile, one of the patients with MET amplification (12 copies) was treated with crizotinib and had regression of liver metastasis and disease control for 5 months (Fig. 3). This finding is consistent with previous results for phase I trials for crizotinib in which two advanced gastroesophageal carcinoma patients with MET amplifications (FISH MET/CEP7 ratio of >2.2) had partial response and stable disease with time to progression of 3–4 months [41].

The comprehensive genomic profiling assay in this series used a process-matched normal control to quantitatively estimate the absolute copies of MET while controlling for ploidy. The threshold of six copies for the designation of MET amplification by FoundationOne in cases with a diploid genome can be translated as exceeding a MET/CEP7 ratio of 2.2 (Fig. 4).

Notably, the comprehensive genomic profiling assay used in this study (FoundationOne) provides quantitative estimates of copy number amplifications (Fig. 4). Copy number estimates made by the genomic profiling assay used do not directly translate to a FISH ratio per se but, as shown by our patient response, provide clinically relevant information that can guide use of targeted therapy (Fig. 3). Comprehensive genomic profiling provides the advantage of simultaneous assessment of many possible clinically relevant copy number amplifications including MET, FGFR2, and ERBB2 while minimizing consumption of the specimen [19]. In contrast, other forms of molecular testing are hypothesis driven, and is, a “hotspot” exon examines only specific exons of genes of interest and is often combined with FISH to assay for amplifications (i.e., ERBB2 and MET). A focused approach offers conceptual simplicity, but for those cases harboring relevant genomic alterations outside the scope of such hotspot testing, genomic profiling could be done to identify potential benefits of targeted therapy instead of expending both time and resources on hotspot testing that might not yield information to guide treatment.

In one of the largest screening studies for KRAS mutations involving GC samples from U.K., Japan, and Singapore, KRAS mutations were found in 29 of 710 GC samples (4.1%). The frequency of KRAS mutations was 5.8% among U.K. patients, 4.0% among Japanese patients, and 1.5% among Singapore Chinese patients. The role of KRAS mutation in GC is unknown, but in this series, KRAS mutations were identified in 16% of GC cases. The most common alterations were G12V (3.4%) and G12D (2.5%), which are both transversions. This most likely reflects a selection bias in this sample population, with patients sent for genomic profiling having poor prognosis and possible KRAS enrichment.
Alterations in the tumor suppressors TP53 and ARID1A are common in gastric cancer. ARID1A encodes the AT-rich interactive domain-containing protein 1A, a member of the SWI/SNF chromatin-remodeling complex. Inactivating alterations in ARID1A are frequent in ovarian clear cell carcinomas, neuroblastomas, and gastric carcinomas and loss of expression in other tumor types, consistent with the hypothesized tumor suppressor role of this protein [43, 44]. Alterations of ARID1A in this series did not cluster around a hotspot (Fig. 2). The statistically significant enrichment of PIK3CA and the paucity of TP53 alterations in the set of ARID1A-altered GCs are consistent with previous findings in gastric carcinoma [43, 45]. In our series, ARID1A-altered cases were also enriched for CREBBP and MLL2 alterations.

Interestingly, our series identified somatic CDH1 mutation rates (25% diffuse, 12% nondiffuse) higher than previously reported (Fig. 5) [46]. The differences in alteration frequency may be related to the interrogation of the entire coding sequence of CDH1 in this assay compared with the limited hotspot assessment of exon 7–10 hotspot interrogation in prior series [46, 47]. CDH1 somatic mutation has been correlated with the shortest survival in GC, and selection bias may underlie increased CDH1 mutation rates in this series because clinicians may be likely to reach for mutational profiling when options are limited [46]. In reporting these results, caveats for directed germline testing are included.

Neither BRAF V600E or V600M alterations previously described in GC were observed in this series, but three nonBRaFV600 mutations were found in this series [13, 48–50] (supplemental online Table 1). The BRAF alterations in these series are variable activators of BRAF.

Interestingly, no alterations in VEGFR1–3 were identified in this series. Ramucirumab has been shown to improve OS in GC in second-line treatment as a single agent or in combination with paclitaxel. Ramucirumab is a monoclonal antibody against VEGFR2, but, like other antiangiogenic therapies, there are no clear predictive biomarkers [51, 52]. Current evidence is insufficient to examine whether VEGFR1–3 alterations serve as biomarkers for ramucirumab.

Identifying clinically relevant alterations in the course of clinical care of gastric carcinoma may drive clinical decisions making, which in turn will generate preliminary data on the efficacy of targeted therapies in gastric carcinoma and care of future patients and will support future systematic investigation through clinical trials. At present, most suggestion of benefit from targeted therapy in gastric carcinoma is guided by analogy to other tumor types. Such reasoning highlights the limitations of this approach, for example, BRAF V600E-mutant colorectal adenocarcinoma has not suggested benefit from vemurafenib monotherapy [53, 54].

Figure 4. Copy number alteration plots for several cases harboring receptor tyrosine kinase amplifications.

Alterations in the tumor suppressors TP53 and ARID1A are common in gastric cancer. ARID1A encodes the AT-rich interactive domain-containing protein 1A, a member of the SWI/SNF chromatin-remodeling complex. Inactivating alterations in ARID1A are frequent in ovarian clear cell carcinomas, neuroblastomas, and gastric carcinomas and loss of expression in other tumor types, consistent with the hypothesized tumor suppressor role of this protein [43, 44]. Alterations of ARID1A in this series did not cluster around a hotspot (Fig. 2). The statistically significant enrichment of PIK3CA and the paucity of TP53 alterations in the set of ARID1A-altered GCs are consistent with previous findings in gastric carcinoma [43, 45]. In our series, ARID1A-altered cases were also enriched for CREBBP and MLL2 alterations.

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Because new approaches such as the combination of vemurafenib and erlotinib confer some benefit to similar patients, as noted, it is hoped that analogous approaches can also benefit gastric carcinoma patients [54].

Conclusion

The high frequency of clinically relevant genomic alterations in this patient population reflective of routine clinical practice is encouraging in a disease that continues to have a poor prognosis with modern chemotherapy. The clinically relevant alterations identified by this assay beyond those detected by standard of care can drive increased clinical trial participation and development (e.g., ERBB2 base substitutions, MET amplifications) and clarify predictive response and resistance biomarkers.

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Final approval of manuscript: Siraj M. Ali, Juliann Chmielecki, Jeffrey S. Ross, Vincent A. Miller

Disclosures

Siraj M. Ali: Foundation Medicine Inc. (E, OI); Eric M. Sanford: Foundation Medicine Inc. (E, OI); Kai Wang: Foundation Medicine Inc. (E, OI); Norma A. Palma: Foundation Medicine Inc. (E, OI); Juliann Chmielecki: Foundation Medicine Inc. (E, OI); Roman Yelensky: Foundation Medicine Inc. (E, IP); Gary A. Palmer: Foundation Medicine Inc. (E, OI); Deborah Morosini: Foundation Medicine Inc. (E, OI); Doron Lipson: Foundation Medicine Inc. (E, OI, IP); Daniel V. Catenacci: Foundation Medicine Inc. (C/A); Fadi Braiteh: Foundation Medicine, Caris Life Sciences, Genomic Health, Molecular Health (C/A); Amgen, Bayer, Pfizer, BMS, Celgene, Insys, incyte, Caris Life Sciences, Genomic Health (H); Rachel Erlich: Foundation Medicine Inc. (E, OI); Philip J. Stephens: Foundation Medicine Inc. (E, OI); Jeffrey S. Ross: Foundation Medicine Inc. (RF, E, OI, IP); Vincent A. Miller: Foundation Medicine Inc. (E, OI). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board
CASE REPORT

A FALSE POSITIVE MECKEL’S SCAN IN A YOUNG WOMAN WITH IRON DEFICIENCY ANAEMIA


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St George’s Hospital, London

Case report

A 40 year old Indian woman who was referred initially to Haematology Clinic having been found to have thrombocytosis with a platelet count consistently above 500x109/l and IDA with a ferritin of 17 µg/l by her general practitioner. On further questioning she described a 3-year history of left iliac fossa pain that was mild and never precipitated her to present to a clinician previously. It had been relieved with non-steroidal anti-inflammatories. She denied any history of vomiting, diarrhoea or constipation. She opened her bowels twice daily, with no report of per rectal bleeding. She also denied fevers, night sweats or a productive cough. There was initially no weight loss although during 2014 she lost 4kg. She denied a loss in appetite. Her periods were regular and she denied them ever being heavy.

Her past medical history included autoimmune thyroiditis for which she took thyroxine replacement therapy. She also had had a superficial abdominal cyst removed at the age of 15 in India. Her only other medication included the combined oral contraceptive pill. She had no family history of note including colorectal cancer. She had moved to the UK in 2010 and visited relatives in India annually. She worked as a nanny and was not vegetarian. Her clinical examination was entirely unremarkable.

The Haematology team had tested her JAK-2 status, which was normal and performed a trephine bone marrow biopsy, which showed normocellular marrow and no evidence of a primary haematological disorder. Her IDA was treated with a Ferinject™ (ferric carboxymaltose) infusion following a failure to tolerate oral replacement.

In view of her normal haematology examination she was referred to the gastroenterology clinic. The patient had a normal coeliac screen and autoimmune screen. An oesophago-gastro duodenoscopy (OGD) was performed which was macroscopically normal, with normal duodenal biopsies. As per BSG guidelines at this stage lower GI endoscopy was performed which was macroscopically circumferential caecal ulceration involving the ileo-caecal valve, endoscopically thought to be consistent with Crohn’s disease with the terminal ileum appearing normal. The terminal ileum showed sparse superficial acute inflammation. Caecal biopsies showed ulceration with granulation tissue. Focal cryptitis and occasional crypt abscesses were present. Occasional loose non-necrotising granulomas and multinucleate giant cells were seen. Ziehl-Neelsen and fungi staining were negative as was immunostaining for cytomegalovirus. However, despite a negative acid-fast bacilli microscopy, Mycobacterium tuberculosis was isolated after 16 days of incubation with the tuberculosis polymerase chain reaction sent also returning positive for Mycobacterium tuberculosis. The patient was referred to the TB team and was commenced on quadruple therapy (Rifampicin, Pyrazinamide, Ethambutol, Isoniazid) for abdominal tuberculosis. At follow up her abdominal symptoms have all resolved.

Discussion

Iron deficiency anaemia affects 800 million people worldwide and is a common problem that affects pre-menopausal women.1 IDA in this demographic is often attributed to menstruation and pregnancy. As a result, guidelines for investigation of pre-menopausal iron deficiency anaemia are not as meticulous as they are in the post-menopausal state when a greater focus is placed on detecting a neoplastic lesion due to the greater incidence of colorectal cancer in women over the age of 50, with 95% of all bowel cancers diagnosed after this age.2

The British Society of Gastroenterology (BSG) published clear guidelines on the management of IDA in 2011.3 As happened with our patient, her coeliac serology was tested which was negative. Because she had vague abdominal pain she proceeded to have an oesophago-duodenoscopy, which was normal. Our patient had initially been referred to Haematology for a thrombocytosis as well as IDA, so her JAK2 status and bone marrow were examined to rule out essential thrombocythaemia. As this patient had no family history of colorectal carcinoma she did not proceed to colonoscopy, and she received appropriate iron replacement therapy.

It was in view of her ongoing non-specific lower abdominal pain and IDA despite iron replacement that a Meckel’s scan was organised to rule out a Meckel’s diverticulum. Meckel’s scans are used to detect the ectopic gastric mucosa in patients with symptomatic Meckel’s diverticulum. Utilising the physiological mimicry that exists
with ectopic gastric mucosa secreting chloride into the intestinal lumen, Technetium-99m ($^{99m}$Tc) pertechnetate acts as an analogue of chloride. This allows the radiolabelled isotope to be secreted into the intestinal lumen, which is highlighted on a scan. 4-6 Our patient had a positive scan within the terminal ileum/caecum, with a radiological report commenting that this could indeed be a false positive result, reflecting underlying Crohn’s disease, given the history of abdominal pain and IDA. Meckel’s scans have a specificity of 95% and sensitivity of 85% however this diminishes after adolescence. 7 False positive Meckel’s scans have a wide differential. Any tissue containing ectopic gastric mucosa will be detected on scan. Focal small bowel pathology such as Crohn’s, abdominal abscesses or intussusception can be highlighted. It is hypothesised this is related to localized hyperaemia associated with these conditions. 4-7 Other causes include neoplastic lesions e.g. colorectal carcinoma, leiomyosarcoma, ileal carcinoid and vascular malformations such as haemangiomas and A-V malformation. As $^{99m}$Tc pertechnetate is excreted renally, genito-urinary false positive foci such as an extrarenal pelvis, horseshoe kidneys, ureteric obstruction can be falsely identified as a positive result. Occasionally iatrogenic causes such as laxatives and endoscopy can causes false positive results, again postulated to be due to hyperaemia caused by localized inflammation. 7 Following the Meckel’s scan, the decision to perform colonoscopy was taken. This identified caecal ulceration which whilst macroscopically looking like Crohn’s disease, cultures and PCR identified underlying abdominal TB. This has never previously been documented as a cause of false positive Meckel’s scan result. It is hypothesised that was likely caused by the chronic inflammation creating a localised hyperaemia. Abdominal TB needs to be considered within the differential of alternative causes for a false positive Meckel’s scan in any patient that has travelled from an area of endemic TB.

This case also poses the question regarding colonoscopy in young women and whether it should have been performed earlier, given that it elucidated the aetiology of this patient’s pathology through cultures and PCR of the lesion. This is a controversial topic, not least because sinister diagnoses like colorectal carcinoma in pre-menopausal women are an elusive diagnosis and an emotional topic. 8 BSG guidelines highlight that dual upper and lower GI pathology, while uncommon, does occur in 1-10% of patients. 9-11 Whilst recto-sigmoid colorectal carcinoma remains the commonest tumour, 12 younger patients, especially those with ascending colon cancers, often present late. 13

Figure 1. Images of Meckel’s scan performed. $^{99m}$Tc Technetium production seen within stomach but also noted in right iliac fossa, initially thought to be consistent with a Meckel’s diverticulum. Increased contrast also seen bladder, related to renal excretion of contrast.
As is such, there is a growing voice of bi-directional endoscopic assessment in pre-menopausal women who present with IDA. Current BSG guidelines do not advocate colonoscopy in pre-menopausal women without a strong family history of colorectal carcinoma (two affected first-degree relatives or just one first degree relative affected before the age of 50 years) or colonic symptoms, neither of which this patient had. It should be noted that colonoscopy is not without its risk with an albeit low risk of perforation around 0.01%. It remains to be seen if other forms of colonic assessment are considered in future. CT colography is inappropriate in the pre-menopausal state due to high doses of radiation, whilst other alternatives such as capsule endoscopy may be considered, although sensitivities for detection of polyps >6mm vary anywhere from 63 – 89% and specificities ranging from 64-94%. It does however remain a cost effective and relatively risk free alternative option.

Summary

IDA assessment in pre-menopausal women who are negative with vague abdominal symptoms remains a controversial topic regarding bidirectional endoscopic assessment. In more ambiguous presentations like with our patient, a lower threshold for colonoscopy should be considered.

Abdominal TB is a new recognised cause of a false positive Meckel’s scan and should be considered in any patient who is from, or has returned from, an area of endemic TB.

References:

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Resolor® (prucalopride) Selective serotonin (5-HT4) receptor agonist, enterokinetic agent, available as 1 mg and 2 mg film-coated tablets for oral administration once daily, with or without food, at any time of the day. 

INDICATION: Resolor is indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.

DOSE: Women: 2 mg once daily. Older people (65 years): Start with 1 mg once daily, and increase to 2 mg once daily if necessary. Patients with severe renal impairment (GFR < 10 ml/min/1.73 m2) 1 mg once daily. Patients with severe hepatic impairment (Child-Pugh class C) start with 1 mg once daily which may be increased to 2 mg if required to improve efficacy and if the 1 mg dose is well tolerated. No dose adjustment required in patients with mild to moderate renal or hepatic impairment. Men: the safety and efficacy of Resolor has not been established in controlled clinical trials, therefore Resolor is not recommended for use in men until further data becomes available. Do not use in children and adolescents younger than 18 years.

CONTRAINDICATIONS: Hypersensitivity to prucalopride or any of the excipients. Renal impairment requiring dialysis, severe inflammatory conditions of the intestinal tract, such as Crohn’s disease, and ulcerative colitis or toxic megacolon in pregnancy. PRECAUTIONS: Caution should be exercised when prescribing Resolor to patients with severe hepatic impairment (Child-Pugh class C) due to limited data in patients with severe hepatic impairment. The safety and efficacy of Resolor for use in patients with severe and clinically unstable concomitant disease (e.g. cardiovascular or lung disease, neurological or psychiatric disorders, cancer or AIDS and other endocrine disorders) have not been established in controlled clinical trials. Caution should be exercised when prescribing Resolor to patients with these conditions especially when used in patients with a history of arrhythmias or ischemic cardiovascular disease. In case of severe diarrhea the efficacy of oral contraceptives may be reduced and an additional contraceptive method is recommended. Contains lactose monohydrate. Patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption must not take Resolor. INTERACTIONS: Prucalopride has a low pharmacokinetic interaction potential. Studies in healthy subjects did not show a clinically relevant effect of prucalopride on the pharmacokinetics of warfarin, disopyramide, alcohol, paroxetine or oral contraceptives. A 39% increase in plasma concentrations of erythromycin was found during prucalopride co-administration. The mechanism for this interaction was not clear. Prucalopride increased the systemic exposure to prucalopride by 40%. This effect is too small to be clinically relevant. Therapeutic doses of probenecid, cimetidine, erythromycin and paroxetine did not affect the pharmacokinetics of prucalopride.

PREGNANCY: Women of childbearing potential should use effective contraception during treatment with Resolor. Animal studies did not indicate harm. Experience of Resolor during human pregnancy is limited. Cases of spontaneous abortion have been observed in human clinical studies, although in the presence of other risk factors, the relationship to Resolor is unknown. Resolor is not recommended during pregnancy. LOCATION: Prucalopride is excreted in breast milk; however, as therapeutic doses no effects are anticipated on the breastfed newborn/infant. In the absence of human data Resolor is not recommended during breastfeeding. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: No studies have been performed. Resolor has been associated with dizziness and fatigue, particularly on the first day of treatment, which may affect driving or using machines.

SIDE EFFECTS: The most commonly reported side effects in Resolor clinical trials were headache and gastrointestinal symptoms (abdominal pain, nausea, diarrhoea) occurring in about 10% of patients each. These events occur mostly at the start of therapy and usually disappear within a few days while continuing Resolor. Other common adverse events in controlled trials included dizziness, vomiting, dyspepsia, rectal haemorrhage, flatulence, abdominal bloating, constipation and fatigue. Concomitant adverse events included anorexia, tremor, palpitations, fever and malaise. After the first day of treatment the most common adverse events were reported with similar frequency for Resolor and placebo except nausea and diarrhoea: these adverse events were reported with similar frequency for Resolor and placebo except nausea and diarrhoea: these events remained higher but the difference between Resolor and placebo was smaller (1 to 3%). Palpitations were reported in 2.7% of placebo patients, 3.0% of 1 mg Resolor patients and 5.9% of 2 mg Resolor patients. As with any new symptom, patients are advised to discuss new onset palpitations with their physician. PACK SIZE AND BASIC NHS PRICES: 28 tablets (4 blisters with 7 tablets) EU/1/09/581/001 (1 mg) £18.69, EU/1/09/581/002 (2 mg) £19.52. LEGAL CATEGORY: POM. MANUFACTURER: Shire Pharmaceuticals Ireland Limited, 33 North Great George’s Street, Dublin 2, Ireland. DATE OF PREPARATION: 15 December 2010. Further information is available on request from Shire plc, Uxbridge. A full Summary of Product Characteristics before prescribing, particularly in relation to hypersensitivity to any of the constituents, renal impairment requiring dialysis, intestinal perforation or obstruction, obstructive ileus, severe inflammatory conditions of the intestinal track, severe and clinically unstable concomitant diseases. 

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AN UNUSUAL CASE OF BREATHLESSNESS: HEPATIC HYDROTHORAX

M Moore; S Chatu; A Saxena

Kings College Hospital, London, UK

Key Words: Chronic liver disease, pleural effusion, hepatic hydrothorax, refractory hydrothorax, cirrhosis

Case:

A 48 year old lady known to have compensated cirrhosis from alcohol misuse of Child Pugh grade B severity presented with a one week history of worsening breathlessness rendering her dyspnoeic at rest.

She did not report a cough, haemoptysis, fevers or chest pain and there was no history of primary cardio-respiratory disorders. There was no history of lower limb swelling or abdominal distension.

On examination she was breathless at rest. Her oxygen saturations were 93% despite FiO2 of 60%. Her respiratory rate was 35 breaths per minute, pulse rate 86 and blood pressure was 152/83 with no pyrexia. There were peripheral stigmata of chronic liver disease. Respiratory examination revealed reduced expansion of the right hemi-thorax, with dull percussion note, reduced air-entry and reduced whistling pectoriloquy. The trachea was deviated to the left. Heart sounds were normal; there was no ascites or lower limb oedema.

Subsequent investigations included an arterial blood gas (ABG) revealing type 1 respiratory failure with a pH 7.47, PO2 9.31 and PCO2 3.80 on supplemental oxygen with FiO2 of 60%. Laboratory results revealed a CRP of 8.6 (normal ranges in brackets), WBC 12.24, eGFR >90 INR 1.52 and Bilirubin 170, ALP 121 AST 127 and gamma GT 98. A chest x-ray (figure 1) demonstrated a complete whiteout of the right lung consistent with a large right-sided pleural effusion with contralateral mediastinal shift.

An ultrasound (USS) of the thorax confirmed a massive pleural effusion (figure 1). Consequently, a 12F Seldinger chest drain was inserted which drained 5 litres of fluid. Fluid analysis revealed a transudate with protein 3g/l, M.C&S, AFB stain and cytology were negative. The pH was 7.5 making an empyema unlikely. Following drainage of the pleural effusion the patient’s breathlessness resolved.

A repeat chest x-ray was performed (figure 2) demonstrating effective drainage of the pleural effusion. Liver USS confirmed cirrhosis but there was no evidence of ascites, portal vein thrombosis or hepatocellular carcinoma. A CT chest was subsequently ordered excluding any underlying pulmonary pathology. An oesophagogastroduodenoscopy (OGD) demonstrated oesophageal varices and mild portal hypertensive gastropathy. A gastroenterology opinion was sought and evaluation led to a diagnosis of a right hepatic hydrothorax.

Diuretics were commenced in addition to chest drain insertion. The patient was started on dual diuretic therapy that included spironolactone 50mg and furosemide 40mg, which was up titrated every 3 days to a dose of 200mg and 120mg, respectively. Since the patient remained well she was discharged with planned follow-up in the gastroenterology clinic. At follow-up there was no reoccurrence of her effusion and she is no longer on diuretic therapy.

Discussion and review of the literature

This case demonstrates an atypical presentation of an uncommon condition. Hepatic hydrothorax is another manifestation of extracellular fluid accumulation in patients with liver cirrhosis in addition to ascites. Due to the lack of large randomized-controlled trials, the prevalence of hepatic hydrothorax has been estimated to be between 5-6%. This has been based on an assortment of varying frequencies being reported, such as autopsy and case reports.

Defining features include established liver cirrhosis from any cause in the context of a transudate pleural effusion > 500ml with no primary cardiopulmonary disease. Concurrent ascites has been reported in up to 84% of cases, making this an altogether rarer presentation. Our patient had a right pleural effusion which is in keeping with the literature since this is the case in the majority of patients.

There are several proposed mechanisms in the development of a hepatic hydrothorax. The pathogenesis is thought to be the same as developing ascites. It has been suggested that hypoalbuminaemia, azygos vein hypertension and arterial splanchnic dilatation all cumulatively contribute to fluid accumulation. Arterial splanchnic dilatation causes a fall in arterial blood volume, creating an accumulation of fluid. Consequent activation of the renin-angiotensin-aldosterone system causes activation of sympathetic nervous system and vasopressin release.

These mechanisms do not explain the predilection to the right lung, nor the absence of ascites. This has been attributed to diaphragmatic defects categorised into four morphologies. This includes small herniations, called pleuropertoneal blebs, which create communications between the peritoneal and pleural cavities. The right hemi-diaphragm is not as muscular and robust as the left; blebs are also more common on the right side. Negative intrathoracic pressure during inspiration causes a migration of fluid. Hydrothoraces occur when the pleural membranes exceed their capacity to absorb the fluid creating the effusion.
Initial management in this case was symptom control. The constrictive nature of the pleural cavity means a small amount of fluid can cause dramatic symptoms, unlike ascites where many litres of fluid may accumulate. This patient drained an impressive 5 litres. Therapeutic thoracentesis is the most effective method for symptom relief. Current evidence shows that hydrothoraces tend to recur rapidly post drainage removal. This, coupled with the infection risk associated with chest drains, meant other treatment options available were sought.

As the pathophysiology behind a hydrothorax is the same as ascites, medical management is unchanged. Sodium restriction and excretion achieved by diet modification and diuretics is the mainstay of treatment. High doses of spironolactone and furosemide are effective means of diuresis, however in refractory hydrothorax, transjugular intrahepatic portosystemic shunt (TIPS) is an alternative. Unfortunately patients with hepatic hydrothorax have limited survival with only favourable survival rates associated with those that have a liver transplant. Hepatic hydrothoraces are a manifestation of end-stage liver disease, regardless of the primary pathology. The only definitive treatment for this is a liver transplant. Due to the rare nature of this condition there are few studies that have looked at transplantation for patients with hepatic hydrothorax, uncomplicated or complicated. Despite this, the evidence shows that transplantation is the best therapeutic option for permanent resolution of hepatic hydrothorax, and has been associated with significant long-term survival rates.

Conclusion

This case demonstrated a rare presentation of hepatic hydrothorax. It is important for any clinician on the medical take to consider this manifestation in known or suspected patients with cirrhosis presenting with a unilateral pleural effusion. Early recognition and awareness, including involvement of the multidisciplinary team, can ensure prompt treatment and avoidance of unnecessary investigations.

Reference:

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Prescribing information and references can be found overleaf.
As a medical student, I learned about Coeliac Disease (CD), alongside cystic fibrosis, as diseases of failure to thrive in children. Today it is a genetically determined autoimmune condition characterized by small-intestinal mucosal injury and nutrient malabsorption. It is activated in genetically susceptible individuals by the dietary ingestion of proline- and glutamine-rich proteins that are found in wheat, rye, and barley and are widely termed "gluten". The world seems to have woken up to the problems of sensitivity to wheat protein or gluten and from my personal experience is not only a diagnosis made by healthcare professionals to explain malabsorption, but is also a fashion label of self-diagnosis used by individuals who truly find that there is something about wheat that does not agree with them or may be found that making themselves special fills a gap in their lives.

The conference that I attended reported some outstanding science, which progresses the diagnosis, management and potentially the prevention of the condition.

Professor Ludvig Sollid from the centre for Immune Regulation, Oslo, reviewed the national behind novel therapies in CD. CD is a prevalent polygenic disorder caused by a harmful immune response to gluten – wheat protein (gliadin). The single most important genetic factor is the major histocompatibility complex (MHC) and the association with HLA DQ2.5, DQ2.2 and DQ8. If these are not present, then the risk of CD is low. These HLA molecules present gluten epitopes to CD4+ T cells. Gluten epitopes then are digested by the enzyme transglutaminase 2 (TG2) and CD patients have autoantibodies to this enzyme which are produced when there is consumption of wheat. There are a variety of peptides that CD patients should avoid. The genetic control is probably in lymph nodes/Peyer’s patches. This offers a potentially interesting target for therapy e.g. modulating T cell effector function.

There are a number of potentially preventative options such as given modification so that the peptides are not recognized by relevant T cells, polymer binding to gluten, specific enzyme that will cleave gluten, epithelial barriers preventing contact and TG2 inhibitors. Treatment options suggested from the knowledge of the mechanism could involve modification of the immune response e.g. cytokine release. The promise for specific therapies for this immune response is there.

Dr Bob Anderson, Chief Scientific Officer of Immunosant, Cambridge, MA, USA presented on therapy and diagnosis of CD using peptides recognized by gluten-reactive T cells. Since 2006, his focus has been on utilizing the most dominant peptides recognized by T-cell in CD using diagnostic blood tests (rather than jejunal biopsy) and to restore immune tolerance to gluten with adjuvant free 'epitope specific' immunotherapy. He reminded the audience that CD is a systemic disease triggered by gluten, but not a single entity gluten. The Enzyme-Linked ImmunoSpot (ELISPOT) assay is a widely used method for monitoring cellular immune responses in humans and has identified 2 dominant gliadin peptides after a 3 day oral gluten challenge and Nexvax2 is a therapeutic vaccine that combines three proprietary peptides that elicit an immune response in patients with coeliac disease who carry the immune recognition gene HLA-DQ2. In an approach similar to treatments for allergies to dander from cats and dust mites, Nexvax2 is designed to reprogram gluten-specific T cells triggered by the patient’s immune response to the protein. The goal is for Nexvax2, epitope specific immunotherapy for CD patients, delivered intradernally,
to restore celiac patients’ immune tolerance to gluten, reduce inflammation in the nutrient-absorbing villi that line the small intestine, return the intestine to a healthy state, and allow patients to eat a normal diet. (It is noted that there are other immunotherapies in development by a variety of companies, but at the time of writing none have successfully completed phase III studies.)

Dr Daniel Adelman, Chief Medical Officer at Alvine Pharmaceuticals, Inc. from San Francisco presented information on gluten degradation by ALV003, a novel drug candidate for CD. He reminded the audience that at the moment the only treatment option for CD is a lifelong adherence to a gluten free diet (GFD), but this brings with it many complications and limitations to normal life quality. Villous height/crypt depth ratio is an important marker of success in management of CD and based on this outcome, it seems that GFD may not be a totally adequate answer. A recent abstract in Gastroenterology tells us that ALV003 consists of 2 co-administered gluten-specific proteases, ALV001 and ALV002. ALV001 is a modified recombinant version of the proenzyme version of cysteine endoprotease, EP-B2, derived from barley. In vitro studies have shown that ALV001 proteolyses gluten adjacent to glutamine residues, and ALV002, a modified recombinant version of prolyl endopeptidase from the bacterium Sphingomonas capsulate (SC-PEP), proteolyses the peptide products of ALV001 digestion by cleaving adjacent to proline residues. Together these enzymes degrade gluten more rapidly and thoroughly than either enzyme alone. ALV003 proteolyses various forms of gluten such as purified gliadin (as well as secalins and hordeins), uncooked gluten flour and whole-wheat bread gluten, eliminating >90% of the immunoreactive epitopes in vitro. The treatment is envisaged as an adjunct to GFD. According to the paper in Gastroenterology, based on a phase 2 trial, the glutenase ALV003 appears to attenuate gluten-induced small intestinal mucosal injury in patients with CD in the context of an everyday gluten-free diet containing daily up to 2 g gluten.

Dr Elena Verdu, Associate Professor, Department of Medicine, McMaster University, Canada discussed ‘What is elafin and does it play a role in gluten related disorders?’

Elafin is an immunomodulatory serine protease inhibitor found in epithelial surfaces and has a potent inhibitory effect against various forms of pro-inflammatory elastases as well as proteinase-3. It shows an abnormally low expression in IBD patients. It was thought that elafin might have a value as an adjunct to GFD in CD as elafin expression in the epithelium of CD patients is lower than in controls, and in an animal model, elafin has been found to decrease inflammation. The work at the moment is theoretical, but it was thought that work on elafin might lead to further knowledge about the mechanisms of CD.

Dr Luud JWJ Gilissen, researcher at Wageningen University and research centre, The Netherlands told the audience about plant and food technological approaches to reduce the incidence of CD. He said that about 2% of the population are ‘wheat sensitive’, which may not be surprising as there are about 30 proteins in wheat and changes in breeds have increased the number of identifiable proteins and hence there is also non coeliac wheat sensitivity. There is a correlation, she said, with irritable bowel syndrome, with 30% improving on a GFD and the Low FODMAP Diet (FODMAP=Fermentable Oligo-Di-Monosaccharides and Polyols). FODMAPs are carbohydrates (sugars) that are found in foods. Not all carbohydrates are considered FODMAPs but spelt wheat is low in FODMAPs. Apparently, there is wheat content in 30% of supermarket foods but that which is in bread, has been genetically selected and currently the search is on for synthetic hexaploid wheats where it may be possible to reduce or separate gliadin. It is interesting to note that sourdough breads, popular in Germany are safe for CD patients as there is breakdown of the culprit peptides in the bakery process.

He suggested a number of potential strategies to reduce the incidence of CD, including:

- Improvement of the GFD so that the health of individuals with persistent symptoms and villous atrophy despite adherence to a GFD.
- Plant related strategies including the search for CD low immunogenic wheat varieties and silencing the expression of gluten gene families
- Reduced use of gluten as a bread improver and improving processed foods to eliminate the highly CD immunogenic gliadin fraction
- The use of alternative grains as CD patients can tolerate uncontaminated gluten-free oats as none of the gluten epitopes known from wheat, barley and rye occur in oats.

It was concluded that the potential for these strategies depended on the cooperation of food breeders, the food industry and governments to better balance wheat with human health and food safety.

Coeliac UK is committed to supporting research, and the conference gave an update of the future of the condition. There is now a clearer understanding of the causes of CD and the mechanisms involved. As well as the traditional GFD, there are now potential immunotherapeutic and enzyme active agents which have the potential to allow CD patients to access a normal diet, but none of the therapies are approved for prescribing yet. These will function best in the context of specific and convenient diagnostics to identify CD by serological testing. As well as the preventative therapeutic measures, there are dietary approaches involving modification of wheat and use of non-wheat cereals that are devoid of gliadin.

Martin Goldman

References

Glutenase ALV003 Attenuates Gluten-Induced Mucosal Injury in Patients With Celiac Disease, Gastroenterology, June 2014 Volume 146, Issue 7, Pages 1649–1658
Immunosant and Alvine Pharmaceuticals websites.
KARL STORZ is a fairly recent entrant into the GI flexible video endoscopy market although the company has been making flexible endoscopes for other disciplines for many years. Well known as a market leader in surgical rigid endoscopy and imaging systems, KARL STORZ has recently launched their new generation ‘SILVER SCOPE’ GI video endoscope range into the UK market and has linked this launch to their latest modular endoscopic HD camera system – IMAGE1 SPIES™.

Looking at the GI SILVER SCOPE® range the most obvious visual differences are the silver grey ergonomically designed control bodies with their ‘silk touch’ coating, however the design improvements are more than merely aesthetic:

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A routine colonoscope with a 160cm long graduated stiffness insertion tube ideally suited to colonoscopy, even for patients under general anaesthetic whose position cannot be changed during the procedure. It has a generous 3.8mm channel which gives excellent suction even with an accessory in place.

Like most colonoscopes this instrument features a forward pointing jet channel for mucosal washing however unlike other colonoscopes the jet channel in the KARL STORZ SILVER SCOPE® colonoscope is fully brushable during cleaning to avoid blockages and help maintain optimal hygiene levels.

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IMAGE1 SPIES™ is the latest evolution of HD camera systems from KARL STORZ. SPIES™ features a unique modular design which enables it to be tailored to the customer’s specific requirements and easily integrate new technologies. It can be configured in numerous ways to meet the requirements of the customer.

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- IMAGE1 X-LINK™ - Flexible scope module compatible with the majority of KARL STORZ flexible video endoscopes for multiple disciplines including GI
- 3D 1080P FULL HD surgical camera module – providing the latest HD 3D surgical image

A single IMAGE1 camera system can therefore include any three of the Link modules allowing, for example, a colonoscope to be used at the same time as the laparoscopic camera with both images being displayed together in a number of on screen picture-in-picture formats.

The system also boasts the STORZ PROFESSIONAL IMAGE ENHANCEMENT SYSTEM (SPIES™) which allows a number of different enhancement functions to be accessed to further expand the imaging capabilities of the system, not to mention the ability to perform endoscopic procedures using fluorescence imaging techniques.

Whether the IMAGE1 SPIES™ camera is mounted on a Videocart as part of a mobile camera system or is built into a KARL STORZ OR1™ Integrated operating theatre, it is one of the most versatile and sophisticated endoscopic imaging systems available. It can be configured to be equally at home in the operating theatre, endoscopy unit or a clinic location performing everything from flexible sigmoidoscopy screening to the most complex 3D laparoscopic colorectal surgery.

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Dutch scientists build colon cancer progression model

Utrecht, April 30, 2015 - Scientists from the Hubrecht Institute and the University Medical Center Utrecht (UMC Utrecht) have developed a cell culture model of human colon cancer progression. This model mimics the situation in patients more closely than any other colon cancer model so far. It enables researchers to study processes involved in colon cancer development and find new cancer drugs. The work by Clevers and colleagues is published online in Nature this week.

Colon cancer is one of the most common and deadly forms of cancer. Like all cancers, it arises through an accumulation of DNA changes (mutations) in the cell's genome (the genetic information in a cell). In contrast to healthy cells, many colon cancer cells have very unstable genomes and generally contain hundreds to thousands of mutations. This makes it difficult to determine which mutations are essential for cancer development and survival. Those mutations could be targeted for therapeutic intervention. However, until now no good human model systems to study such mutations exist.

Organoids
The recent development of the organoid technology by the research group of Hans Clevers allows the culturing of healthy human tissues under laboratory conditions. Organoids functionally recapitulate the organ of origin and are genetically stable. Utilizing this technology, the Clevers lab has now successfully engineered a colon cancer progression model in organoids from human small intestine and colon.

Genome editing
Jarno Drost, researcher in Hans Clevers’ research group, and his colleagues utilized the genome editing system CRISPR/Cas9 to introduce specific mutations in four of the most commonly altered genes in colon cancer (KRAS, APC, TP53 and SMAD4) and performed an in-depth analysis on their contribution to cancer development. Drost and colleagues showed that mutating these four genes is sufficient to convert a healthy intestinal cell into an invasive tumor cell. The model published in Nature can be used to study processes involved in colon cancer development and for cancer drug discovery.

Reference

Genomic Profiling of Gastric Cancer Identifies Drug-Targetable Mutations

Durham, NC – The majority of gastric cancers harbor genomic alterations (GAs) associated with potential benefit from targeted therapies, according to a new study published in The Oncologist on April 16, 2015. These findings suggest a role for genotype-directed management of locally advanced and metastatic gastric cancer.
To date, the ERBB2 amplification is the only GA in advanced gastric cancer associated with a survival benefit in response to targeted therapy. However, because most patients with gastric cancer do not harbor this rare alteration, most cannot benefit from targeted therapy under current practice guidelines.

To identify additional opportunities for targeted therapy, a team of researchers led by Siraj M. Ali, MD, PhD, at Foundation Medicine, Inc., in Cambridge, MA, conducted comprehensive genomic profiling of patients with locally advanced or metastatic gastric cancer. The goal was to identify clinically relevant GAs, defined as alterations that are currently targetable with therapies approved in gastric cancer or other tumor types, or with therapies currently under development and administered in clinical trials.

“Our study demonstrates the potential utility of comprehensive genomic profiling to match patients to targeted therapies of specific potential benefit in clinical trials,” Dr. Ali said. “This is encouraging in a disease that continues to have a poor prognosis with modern chemotherapy.”

The research team performed comprehensive genomic profiling on 116 gastric cancer specimens harvested from patients with primarily (90.0%) locally advanced or metastatic disease. Thus, the tumor samples were characteristic of gastric carcinomas seen in clinical practice, where the majority of patients present with advanced disease.

The genomic profiling assay detected 501 alterations in 116 samples. Of these, 201 alterations (41%) were clinically relevant, yielding 1.8 drug-targetable GAs per case. In total, 78% of all gastric cancer samples harbored at least 1 clinically relevant GA associated with approved or investigational targeted therapies.

The most common clinically relevant GAs were KRAS (16%), CDKN2A (14%), CCND1 (9.5%), ERBB2 (8.6%), and PIK3CA (8.6%). Other common alterations that are currently not associated with approved or investigational targeted therapies included TP53 (50%), ARID1A (24%), and CDH1 (15%). Many current and emerging targeted therapies used in other tumor types are directed to known alterations in receptor tyrosine kinase (RTK) signaling pathways. In the current series, 1 in 5 gastric cancer cases (20.6%) harbored alterations in RTKs such as ERBB2, FGFR2, and MET.

According to the study authors, comprehensive genomic profiling may be used as a tool for identifying appropriate therapy. One patient with MET-amplified gastric cancer was treated with crizotinib, an inhibitor of c-MET and ALK RTKs currently approved for the treatment of non-small cell lung cancer. Following crizotinib initiation, the patient had regression of a liver metastasis and disease control for 5 months.

“The high frequency of clinically relevant GAs in a population reflective of routine clinical practice highlights potential therapeutic avenues in a disease with historically low responses to current therapies and overall poor survival,” said Samuel Klempner, MD, a member of the research team. “The patient response to MET inhibition encapsulates the genotype-directed approach and underscores the need for molecularly directed clinical trials to confirm observations such as seen in our study.”

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Precautions: Use once a diagnosis of moderate to severe IBS-C is established. Should prolonged (more than 1 week) or severe diarrhea occur, medical advice should be sought and temporary discontinuation of linaclotide until diarrhea episode is resolved may be considered. Exercise caution in patients prone to a disturbance of water or electrolyte balance such as elderly, patients with CV diseases, diabetes, hypertension; and electrolyte control should be considered. Not recommended in patients with chronic inflammatory conditions of the intestinal tract, such as Crohn’s disease and ulcerative colitis. Elderly: Special attention should be given to these patients and the treatment benefit/risk ratio should be carefully and periodically assessed. Children: Not recommended. Interactions: The efficacy of medicinal products absorbed in the intestinal tract with a narrow therapeutic index such as levothyroxine and oral contraceptives may be reduced. The use of additional contraceptives is recommended. Pregnancy and lactation: It is preferable to avoid the use during pregnancy. Use during breast-feeding is not recommended. Animal studies indicate that there is no effect on male or female fertility. Ability to drive and use machines: None known. Adverse Effects: Very common: diarrhea. Common: abdominal pain, flatulence, abdominal distension, dizziness. Consult SmPC in relation to other side effects. Legal Category: POM. Marketing Authorisation Number(s): EU/1/12/801/002. NHS Cost: (excluding VAT) £37.56 – Carton containing HDPE bottle containing 28 capsules. Marketing Authorisation Holder: Almirall S.A., Ronda General Mitre, 151, 08022 Barcelona, Spain. Further information is available from Almirall Limited, 1 The Square, Stockley Park, Uxbridge, Middlesex, UB11 1TD, UK. Tel: (0)207 160 2500. Fax: (0)208 763 888. Email: almirall@professionalinformation.co.uk Date of Revision: 12/2012. Item code: UKUN1411. References: 1. National Institute of Health and Clinical Excellence. Clinical Guideline 61, February 2015. Available at: www.nice.org.uk/guidance/cg61 Last accessed: April 2015. 2. Rao S, et al. Am J Gastroenterol 2012;107:1714–24. 3. Castro J, et al. Gastroenterology 2013;145(6):1334–46. 4. Chey WD, et al. Am J Gastroenterol 2012;107:1702–12. 5. Quigley EM, et al. Aliment Pharmacol Ther 2013;37(1):49–61. 6. Constella® Summary of Product Characteristics. United Kingdom: Almirall Ltd.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Almirall Ltd.
In addition to driving increased clinical trial participation, identifying clinically relevant GAs in patients with gastric cancer may shape future drug development and research on biomarkers of resistance and therapeutic response.

**Weill Cornell Investigators Discover a New Pathway that Prevents Chronic Inflammation in the Gut**

Investigators Show How Immune Cells are “Educated” Not to Attack Beneficial Bacteria

New York (April 23, 2015) -- An international research team led by Weill Cornell Medical College investigators has discovered an answer to why the human immune system ignores roughly 100 trillion beneficial bacteria that populate the gastrointestinal tract. The findings, published April 23 in the journal Science, advance investigators’ understanding of how humans maintain a healthy gastrointestinal tract, and may provoke new ways to treat inflammatory bowel disease -- including Crohn’s disease and ulcerative colitis -- whose origins have been mysterious and treatment difficult.

The investigators studied T cells -- critical components of the adaptive immune system -- which have the capacity to recognize, eliminate and remember foreign microbes that invade our bodies. T cells are named after the thymus, an organ where they develop and are taught not to attack normal human tissues and organs, leaving them free to target and eradicate disease-causing foreign invaders. One question that had puzzled scientists until now is how these cells learn to ignore beneficial bacteria in the intestine that are also foreign, but not harmful.

In the study, the research team discovered that once they leave the thymus, T cells are again educated in the gastrointestinal tract, or gut, to leave beneficial bacteria alone. This dual education strategy is vital to supporting healthy immune function, the investigators say. Disruption in the pathway that facilitates this education, they add, causes the immune system to attack beneficial bacteria in the intestine, which is often linked to the development and progression of diseases like inflammatory bowel disease, HIV, viral hepatitis, cardiovascular disease, obesity, diabetes and cancer. Therapeutic strategies to promote and boost the activity of this education pathway may be beneficial in treating patients with these chronic inflammatory disorders, the investigators say.

“In many chronic human diseases, the immune system attacks bacteria in the intestine that are normally beneficial. Although we do not yet know whether this is a cause or consequence of these complex diseases, experimental evidence suggests that this inflammatory process contributes to disease progression,” says senior author Dr. Gregory F. Sonnenberg, an assistant professor of microbiology and immunology in medicine and a member of the Jill Roberts Institute for Research in Inflammatory Bowel Disease at Weill Cornell. “Our study demonstrates that there may be an efficient way to eliminate pro-inflammatory T cells in the intestine that attack beneficial bacteria. This would not only help our patients with inflammatory bowel disease, but also might give us clues about how to...”

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treat other chronic inflammatory diseases caused by abnormal T cell responses, such as allergic and autoimmune disorders."

In earlier research, Dr. Sonnenberg and his team identified that a recently discovered member of the innate immune system -- innate lymphoid cells (ILCs) -- critically regulate immune cell interactions with bacteria. These ILCs, and other cells of the immune system, are found in the intestine, which is constantly exposed to and colonized by beneficial bacteria. "There is a physical separation between the immune system and most beneficial bacteria," Dr. Sonnenberg says.

The researchers had previously found that ILCs reinforce a physical barrier between the immune system and intestinal beneficial bacteria, but in this study, they uncovered a new key role for these cells -- that they act like the cells in the thymus that educate T cells.

In a process that developed over evolution, bits of human tissues and organs are introduced to T cells in the thymus so they "know" what not to attack after leaving the organ. Specialized cells in the thymus teach T cells this behavior by interacting with a molecule known as the Major Histocompatibility Complex class II (MHCII). Any T cells with the potential to attack the human body and organs and cause autoimmunity are destroyed before they can leave the thymus. However, T cells with the potential to attack beneficial bacteria are not educated or eliminated in the thymus. It was therefore unclear what stopped these T cells from attacking beneficial bacteria in the intestine.

The scientists found a similar process happening directly within the GI tract, an organ that contains the majority of the body’s total immune system.

"Due to the similarities of what we know happens in the thymus, we have called this new process ‘intestinal selection’,” says first author Dr. Matthew R. Hepworth, a postdoctoral associate in medicine who works in Dr. Sonnenberg’s laboratory. "ILCs also interact with T cells through MHCII machinery to educate T cells in the intestine.

"In the thymus, T cells are educated not to attack our organs," he adds, "and in the GI tract, using ILCs, they are further educated not to attack beneficial bacteria."

Using mice to test their findings, the researchers discovered that ILCs destroy T cells with the potential to attach beneficial bacteria, and that impairing ILC function led to severe intestinal inflammation. Then, with the help of researchers at Children’s Hospital in Philadelphia, the team looked at intestinal biopsies of pediatric patients diagnosed with Crohn’s disease, one of the major forms of inflammatory bowel disease.

“We found ILCs in intestinal biopsies from pediatric patients diagnosed with Crohn’s disease, but they were not functioning properly because, in many cases, they were lacking MHCII machinery, so T cells were not educated to ignore beneficial bacteria,” Dr. Sonnenberg says. "In fact, we found the loss of MHCII correlated with an increase in pro-inflammatory cells from matched biopsies of children with Crohn’s disease. That tells us that this education process may be impaired in patients with inflammatory bowel disease, and that restoring adequate levels of MHCII might help to eliminate pro-inflammatory T cells and reduce chronic intestinal inflammation."

Dr. Sonnenberg says there are likely many causes of inflammatory bowel disease, and other pathways that help control T cells in the gut. "But our work shows a previously unrecognized pathway whereby ILCs educate our immune system not to attack beneficial bacteria," he says.

Dr. Sonnenberg, his laboratory and the Jill Roberts Institute for Research in IBD are now exploring how scientists can utilize this knowledge and design novel therapeutic strategies to boost MHCII on ILCs and limit chronic intestinal inflammation.

Co-authors include Thomas C. Fung from Weill Cornell Medical College; Terri M. Lauffer from the University of Pennsylvania; Samuel H. Masur, Judith R. Kelsen and Robert N. Baldassano from Children’s Hospital of Philadelphia; Fiona M. McConnell and David R. Withers from University of Birmingham, United Kingdom; Juan Dubrot, Stephanie Hugues and Walter Reith from the University of Geneva Medical School in Switzerland; Michael A. Farrar from the University of Minnesota; Gerard Eberl from Institut Pasteur, France; and Charles O. Elson from the University of Alabama at Birmingham.

Research in Dr. Sonnenberg’s laboratory is supported by the National Institutes of Health (DP5OD012116), the NIAID Mucosal Immunology Studies Team (MIST), Scholar Award in Mucosal Immunity and the Institute for Translational Medicine and Therapeutics, Transdisciplinary Program in Translational Medicine and Therapeutics (UL1-RR024134 from the U.S. National Center for Research Resources). Other investigator support includes a research fellowship from the Crohn’s, and Colitis Foundation of America (CCFA, #297365), a Cancer Research Institute Student Training and Research in Tumor immunology (StaRT) grant, a Wellcome Trust Research Career Development Fellowship, and the National Institutes of Health (DK071176).

Weill Cornell Medical College
Weill Cornell Medical College, Cornell University’s medical school located in New York City, is committed to excellence in research, teaching, patient care and the advancement of the art and science of medicine, locally, nationally and globally. Physicians and scientists of Weill Cornell Medical College are engaged in cutting-edge research from bench to bedside aimed at unlocking mysteries of the human body in health and sickness and toward developing new treatments and prevention strategies. In its commitment to global health and education, Weill Cornell has a strong presence in places such as Qatar, Tanzania, Haiti, Brazil, Austria and Turkey. Through the historic Weill Cornell Medical College in Qatar, the Medical College is the first in the U.S. to offer its M.D. degree overseas. Weill Cornell is the birthplace of many medical advances – including the development of the Pap test for cervical cancer, the synthesis of penicillin, the first successful embryo-biopsy pregnancy and birth in the U.S., the first clinical trial of gene therapy for Parkinson’s disease, and most recently, the world’s first successful use of deep brain stimulation to treat a minimally conscious brain-injured patient. Weill Cornell Medical College is affiliated with NewYork-Presbyterian Hospital, where its faculty provides comprehensive patient care at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. The Medical College is also affiliated with Houston Methodist. For more information, visit weill.cornell.edu.
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First UK online assessment for Coeliac Disease launched to find the undiagnosed half a million

Coeliac UK, the national Charity for people with coeliac disease, will launch the UK’s first online assessment to help fast track diagnosis among the half a million people in the UK living with undiagnosed coeliac disease.

The online assessment tool is a key initiative of the Charity’s new campaign, ‘is it coeliac disease?’, which is launching in Coeliac UK’s Awareness Week (11-17 May) and backed by the Charity’s new patron, actress Caroline Quentin.

The two year campaign will highlight the most common symptoms of coeliac disease and prompt people experiencing these symptoms to ask themselves, ‘is it coeliac disease?’.

A dedicated website, www.isitcoeliacdisease.org.uk will host the new assessment questionnaire and provide detailed information about coeliac disease and outline the campaign activities.

Based on National Institute for Health and Care Excellence (NICE) guidelines, the new online assessment will give people more confidence to seek further medical advice from their GP. Upon completion of the assessment, they will receive an email with the results which will indicate whether their symptoms are potentially linked to coeliac disease.

Coeliac disease is a serious autoimmune disease where the body’s immune system damages the lining of the small bowel when gluten, a protein found in wheat, barley and rye, is eaten. There is no cure and no medication; the only treatment is a strict gluten-free diet for life. Left untreated, coeliac disease can lead to a number of complications including osteoporosis and in rare cases even small bowel cancer.

Key symptoms caused by coeliac disease include: frequent bouts of diarrhoea, stomach pain and cramping, regular mouth ulcers, ongoing fatigue, lots of gas and bloating, nausea and vomiting, and unexplained anaemia.

One in 100 people in the UK has coeliac disease, with the prevalence rising to one in ten for close family members. However, current statistics show only 24% of those with the condition are diagnosed, leaving an estimated half a million people in the UK undiagnosed.

The ‘is it coeliac disease?’ campaign will also target healthcare professionals to refresh their knowledge of the condition and its symptoms, and will be promoted through radio and digital advertisements, social media activity and information in GP surgeries.

Outreach events will also take place across the country over the next two years providing more information for the general public.
public to ask questions and gain advice from experts. Further details of these events can be found at: www.isitcoeliacdisease.org.uk.

Sarah Sleet, chief executive of Coeliac UK, said:

“With half a million people living with undiagnosed coeliac disease we must take radical action to turn around this horrendous situation. We hope that giving people direct access to an online assessment tool will put those who are suffering with the symptoms of undiagnosed coeliac disease on a pathway to diagnosis and avoid potentially life threatening long term health complications.

As well as help reduce the unacceptable length of time to gain a diagnosis which is currently, on average, 13 years.”

Caroline Quentin, who is close to completing her own diagnosis journey after an initial positive blood test two years ago and more recently a genetic test, said: “Coeliac UK’s campaign to reach the half a million people still undiagnosed with coeliac disease really resonates with me because I struggled for years with constant stomach pains, vomiting and total exhaustion.”

A confirmed medical diagnosis of coeliac disease enables people to receive appropriate follow-up care and support, as well as providing evidence for close family members to also be tested.

Sarah Sleet continued:

“Awareness of coeliac disease has increased greatly in recent years with the Charity’s Helpline supporting hundreds of callers seeking a diagnosis. Yet, around 500,000 people in the UK are still suffering unnecessarily. Please check your symptoms through our online assessment tool, and if you think you may have coeliac disease, go to your doctor and ask for a blood test but don’t stop eating gluten until you are tested otherwise critical follow up tests will not work.”

Ms Sleet said.

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Mezavant XL Safety Information. Mezavant XL is indicated for the induction of clinical and endoscopic remission in patients with mild to moderate ulcerative colitis and for the maintenance of remission. It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and at least twice a year, whilst on treatment. Please consult the Mezavant XL Summary of Product Characteristics before prescribing.

Mezavant XL (mesalazine) Prescribing Information (Please refer to full Summary of Product Characteristics [SmPC] before prescribing).

Presentation: Mezavant XL is available as 1200mg gastro-resistant, prolonged release tablets.

Uses: For the induction of clinical and endoscopic remission in patients with mild to moderate, active ulcerative colitis. For maintenance of remission.

Dosage and administration: Oral. Tablets to be taken once daily. Tablets must not be crushed or chewed and should be taken with food.

Indication: For induction of remission: 2.4g (two tablets) should be taken once daily. The highest dose of 4.8g/day is recommended for patients not responding to lower doses of mesalazine. When using the highest dose (4.8g/day), the effect of the treatment should be evaluated at 8 weeks. For maintenance of remission: 2.4g (two tablets) should be taken once daily. Children: Not recommended.

Contraindications: History of hypersensitivity to salicylates (including aspirin), or other salicylate-containing products, or any of the excipients of Mezavant XL. Severe renal impairment (GFR <30ml/min/1.73m²) or any of the excipients of Mezavant XL. Severe renal impairment (GFR <30ml/min/1.73m²) or any of the excipients of Mezavant XL.

Children: Not recommended.

Special Warnings

Stevens-Johnson syndrome, Drug rash with eosinophilia and systemic symptoms (DRESS), Drug-induced hypersensitivity syndrome and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Shire Pharmaceuticals Ltd on 01256 894000 or at globalpharmacovigilance@shire.com.

Legal category: POM. Marketing Authorisation number: PL 08081/0040.

Marketing Authorisation holder: Shire Pharmaceuticals Contracts Limited, Hampshire International Business Park, Chineham, Basingstoke, Hampshire, RG24 8EP, UK. MEZAVANT is a trademark of Shire Limited in the UK. MMX® is a registered trademark of Cosmo Technologies Ltd, Wollow, Ireland. MMX Multi Matrix System® is a registered trademark of Cosmo S.p.A., Milan, Italy.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Shire Pharmaceuticals Ltd on 01256 894000 or at globalpharmacovigilance@shire.com.


Date of preparation: May 2015. UK/CPROM/MEZ/14/0006b(1).
A model to assess the cost of flare

Ash Bassi1, Keith Tolley1, GW Warner Chilcott2
1Gastroenterology Department, Whiston Hospital, Prescot, Merseyside; 2Tolley Health Economics, UK

Background

• Disease flares of active ulcerative colitis (UC) can result in substantial cost implications to the NHS, affecting both primary and secondary care.5

• In secondary care, flares of active UC are associated with a 2-fold increase in costs for non-hospitalised cases and more than 20-fold increase for hospitalised cases, compared with the maintenance phase.1

• While the costs associated with treatment and management of UC in secondary care are well-documented, estimates of the cost of flare across the spectrum of care pathways are lacking.

• A cost analysis was performed to estimate the healthcare costs associated with managing a flare by modelling resource use across alternative pathways in primary and secondary care.

• This model was then used to estimate costs associated with increased flares, which may result from non-adherence to Asacol® (mesalazine).

Methods

• A decision tree model was developed in Excel to estimate the direct healthcare costs of flares of varying clinical severity.

• The model forms the basis for estimating the average cost of flare in a model cohort, which allows for sensitivity analyses and adapting the model to local patient populations.

• Treatment and management strategies were based on best practice guidelines, published data sources and expert opinion.1

• Drug costs were calculated using the British National Formulary (BNF) and healthcare management costs were based on published unit costs.

• A market forces factor of 1.08 (the UK average) was applied to account for cost differences between healthcare providers due to geographical location.1,4

Costs of UC in remission (base case)

• Within the model, the baseline UC patient cohort was assumed to be maintained on Asacol at a maximum dose of 2.4 g/day, given as 800 mg MR tablets. This is the maximum daily dose recommended for maintenance of remission and provides an upper estimate of the drug costs.3

• Annual management costs for patients in remission were estimated assuming one secondary care consultation per year;1 colonic surveillance every 5 years4 and routine monitoring tests per year, such as full blood count, liver function and renal function tests.1

Costs associated with flare

• Illustrative care pathways were mapped, assuming that patients with a flare of active disease would either be treated and managed in primary care, or as an outpatient, or admitted to hospital.

• Taking a conservative approach, costs for surgery and post-surgical management, e.g. stoma care, were excluded as inclusion would have skewed the data and significantly increased average flare cost estimates.

Average cost of flare

• To calculate an estimated average cost of flare, default values for proportions of patients were assigned to each treatment pathway, based on clinical experience.4

• The default values provide an illustrative example of a model population.

Costs associated with non-adherence

• Using a cohort approach, costs associated with an increase in flare in patients who are non-adherent to Asacol were estimated for a population of 100,000 people (Table 1).

Results

Costs of remission and flare

• The estimated annual cost to manage a patient with UC in remission was £955 (base case; Table 2).

• The additional estimated cost to control a flare in primary care was £175 and for secondary care outpatient management was £578 (Figure 1).

• For secondary care inpatient management, the estimated cost was £3,488 (Figure 1).

• If a biologic/ciclosporin was needed, the estimated cost rose to £4,272 (Figure 1). All costs were inclusive of clinical investigations and treatment reviews.

• Applying the default values for proportions of patients to each of the 3 pathways produced an estimated average cost of flare of £984 in the UC cohort (Table 3).

Adherence analysis

• The estimated annual cost of flare for patients adherent to Asacol and adherent (Figure 2A).

• A potential annual cost saving of £82.33 per patient could be achieved if 5–15% of the patients become non-adherent (Figure 2B).

References

1. Gastroenterology Department, Whiston Hospital, Prescot, Merseyside; 2Tolley Health Economics, UK

2. Annual costs in remission

£955
per patient

*Market forces factor applied

Table 2. Annual costs of ulcerative colitis in remission (base case).

<table>
<thead>
<tr>
<th>Annual drug costs</th>
<th>Management costs</th>
<th>Annual costs in remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>£705.52</td>
<td>£105.00</td>
<td>£810.52</td>
</tr>
<tr>
<td>Per flare (800 mg per flare)*</td>
<td>£5.00</td>
<td>£5.00</td>
</tr>
<tr>
<td>£10.00</td>
<td>£5.00</td>
<td>£15.00</td>
</tr>
<tr>
<td>£6.79</td>
<td>£6.79</td>
<td>£13.58</td>
</tr>
<tr>
<td>£4.73</td>
<td>£4.73</td>
<td>£9.46</td>
</tr>
<tr>
<td>£0.30</td>
<td>£0.30</td>
<td>£0.60</td>
</tr>
</tbody>
</table>

Figure 1. Estimated costs associated with flare in ulcerative colitis

A. Illustrative primary and secondary care pathways for treatment and management of flare; B. break down of costs.

Figure 2. Estimated annual costs associated with non-adherence to Asacol

A. Control of flare; B. Potential cost savings if a proportion of non-adherent patients become adherent.

Table 3. Calculating the average cost of flare

<table>
<thead>
<tr>
<th>Pathway on which flare is managed</th>
<th>Estimated cost per flare</th>
<th>Model (flares)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary care</td>
<td>£125</td>
<td>£7,500</td>
</tr>
<tr>
<td>Secondary care (outpatient)</td>
<td>£144</td>
<td>£9,740</td>
</tr>
<tr>
<td>Secondary care (inpatient)*</td>
<td>£3,880</td>
<td>£61,200</td>
</tr>
<tr>
<td>Estimated average cost of a flare</td>
<td>£5,488</td>
<td></td>
</tr>
</tbody>
</table>

*Market forces factor applied
Costs associated with flare in ulcerative colitis: A. Illustrative primary and secondary care pathways for treatment and management of flare; B. Breakdown of costs.

A

- Annual management costs for patients in remission were estimated.
- A decision tree model was developed in Excel to estimate the direct costs associated with managing a flare by modelling resource use across primary care, or as an outpatient, or admitted to hospital.
- In secondary care, flares of active UC are associated with a 2-fold increase in cost implications to the NHS, affecting both primary and secondary care.
- Disease flares of active ulcerative colitis (UC) can result in substantial costs associated with managing a flare by modelling resource use across primary care, or as an outpatient, or admitted to hospital.

B

- Applying the default values for proportions of patients to each of the treatment pathways produced an estimated average cost of flare of £984 in the UK.
- To calculate an estimated average cost of flare, default values for proportions of patients were assigned to each treatment pathway, 3 pathways produced an estimated average cost of flare of £984 in the UK.
- Crude average of controlled and severe flare was £175 and for secondary care outpatient management was £578.
- A potential annual cost saving of £1,156–£3,468 per 100,000 people could be achieved if 5–15% of non-adherent patients become adherent.
- While further investigation is required to assess real-world validity, this cost model represents a valuable tool for exploring resource utilisation in UC flare management.

### Acknowledgements

This model was developed by Policy Matters LLP and Tolley Health Economics Ltd, sponsored by Warner Chilcott UK Ltd. Editorial support was provided by Avarice Healthcare Communications Ltd, funded by Warner Chilcott UK Ltd.

**References**

3. Bassi A. A decision tree model to estimate the cost of treating a flare of active UC via illustrative primary and secondary care pathways.
4. The findings support the argument for focusing services towards prompt detection and early management of flares to help avoid A&E attendances, unplanned hospital admissions and other costly secondary care resource use.
5. The model considered the cost of UC flare episodes and the potential savings that could be achieved by reducing the incidence and severity of flare episodes.
6. Potentially, the model could help inform decision-making regarding treatment strategies and resource allocation in the management of UC flare.
7. The model was developed to estimate the cost of treating a flare of active UC via illustrative primary and secondary care pathways.
8. The model considered the cost of UC flare episodes and the potential savings that could be achieved by reducing the incidence and severity of flare episodes.
9. The model could help inform decision-making regarding treatment strategies and resource allocation in the management of UC flare.
10. The estimated annual cost of flare per 100,000 people was £5,086 for £1,156–£3,468 per 100,000 people as non-adherent patients became controlled.

### Figure 1

- Estimated costs associated with flare in ulcerative colitis: A. Illustrative primary and secondary care pathways for treatment and management of flare; B. Breakdown of costs.

### Figure 2

- Estimated annual costs associated with non-adherence to Asacol® per 100,000 people: A. Cost of flare for adherent vs non-adherent patients; B. Potential cost savings if a proportion of non-adherent patients become adherent.

Table 1: Estimated annual costs associated with non-adherence to Asacol® per 100,000 people

<table>
<thead>
<tr>
<th>Proportion of patients managed via this pathway</th>
<th>Crude average of controlled and severe flare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherent (30 mg/day)</td>
<td>£175</td>
</tr>
<tr>
<td>Non-adherent (30 mg/day)</td>
<td>£578</td>
</tr>
<tr>
<td>A. £175 per flare</td>
<td>£6.79</td>
</tr>
<tr>
<td>B. £578 per flare</td>
<td>£3,216.51</td>
</tr>
<tr>
<td>Total population</td>
<td>£8.88</td>
</tr>
<tr>
<td>£1,490.50</td>
<td>£8.88</td>
</tr>
</tbody>
</table>

### Table 2: Adherence and non-adherence intervention

<table>
<thead>
<tr>
<th>Adherence intervention</th>
<th>£28,204</th>
<th>£555.69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated number of flares</td>
<td>1.30</td>
<td>0.15</td>
</tr>
<tr>
<td>Estimated reduction in cost of flare</td>
<td>£1,156</td>
<td>£3,468</td>
</tr>
</tbody>
</table>
INTRODUCTION

• In 2000, the UK government introduced the two week rule (TWR) referral initiative. This was to ensure all patients with symptoms potentially indicating a diagnosis of cancer were seen by a relevant specialist within two weeks of referral by their GP.

• The aim was to significantly reduce cancer-related mortality by shortening the time between presentation, diagnosis and treatment.

• Since its initiation, very little data has indicated improved survival outcomes for patients diagnosed with cancer via this pathway.

• Our aim was to evaluate the efficacy of the two week rule service and compare the cancer pickup rate with cost.

METHOD

• All patients presenting to gastroenterology under Two Week Rule (TWR) and standard non-Two Week Rule (non-TWR) pathway were collected over a set 6 week period.

• These patients were prospectively followed up for a 3 month period from date of referral. This was done covertly by the investigators to avoid influencing decision making by the clinic physicians.

• Data recorded included number of clinic visits, number and type of radiological and endoscopic investigations undertaken, end diagnosis and cancer diagnosis.

• Crude costs per patient were calculated using the hospital’s unit costing database.

CONCLUSION

• In our sample of patients, those referred under the two week rule underwent a higher burden of invasive investigation with no significant increase in cancer pickup.

• Of concern, a large proportion of this group did not have a formal diagnosis by after 3 months of follow up.

• We suggest alternative referral pathways to be considered in a bid to improve cancer diagnosis in high risk patients.
The pathway patients indicated treatment between related referral relevant. This was improved significantly by shortening (non TWR) the two week rule gastroenterology referrals at a district general hospital.

**INTRODUCTION**

- Making a decision to undertake endoscopic visits, the service was set to shortening two weeks to avoid costs and mortality by ruling out cancer.

- The number of patients with endoscopic procedure was improved significantly by shortening to two weeks, ensuring potential cancer was detected, although this difference did not reach statistical significance. 23.1% and 19.1% of patients had no clear diagnosis at three months in the TWR and non-TWR respectively.

- There were 52 TWR patients (mean age 72.5) and 89 non-TWR patients (mean age 57.9) (p=0.0001). Female gender represented 51.9% of TWR patients and 64% of non-TWR patients.

- 7.7% of TWR patients and 3.4% of non-TWR patients had an end diagnosis of cancer, although this difference did not reach statistical significance. 23.1% and 19.1% of patients had no clear diagnosis at three months in the TWR and non-TWR respectively.

- The mean cost of investigations and follow-up was significantly higher in the TWR cohort (£754.10 vs £613.10, p=0.04).

**RESULTS AND DISCUSSION**

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**REFERENCES**


AIMS

Increased:

1) Clinical Efficiency
   Reduced costs on establishing the history will speed healthcare allowing larger numbers of patients to be assessed

2) Patient Experience
   More acceptable methodology for asking sensitive questions

3) Patient Safety
   A more comprehensive medical history will protect patients and via an integration engine could feed directly into existing databases and electronic patient records

INTRODUCTION

A number of studies have demonstrated the benefits of touch screen history taking in the primary care setting (Main, Quintela et al. 2004)

This project aims to evaluate the set up of a self directed automated clinic using of a new innovative touch screen program (Pre-Doc™) designed by NHS professionals to establish key parts of a patient’s history. The screen layout is designed to be clear and intuitive and the answers to questions are delivered in an annotated form for rapid reading. We wish to establish whether this technology will provide better clinical information than traditional history taking or paper forms and whether its use can improve clinical efficiency and the patient experience of healthcare.

METHODS

We have developed a large database of questions that could be asked during history taking. A computerised algorithm selects the next relevant question depending on the previous answer. A designer interface allows questionnaires to be developed and adjusted readily. The questions are phrased in plain English, but the program translates the answers into medical terminology. The history is then available in PDF format for presentation to the clinician. Patients self-completed their history using a touch screen, and checked the results before printing. Comments about the process were recorded from patients and clinical staff. The system was trialed in a hepatitis assessment clinic. Patients are fully informed about this voluntary and secure system prior to use.

RESULTS

443 patients used the touch screen. 12 did not complete their history because of language problems (8) or indifference (3). The average time to complete was 14.7 minutes (range 7-21 minutes). 7 patients were identified who were at high risk of hepatitis infection, and a monospot test was offered and accepted in all of these and further serological tests undertaken. 180 patients with known positive serology completed their history for use in a new patient hepatitis outpatients clinic.

CONCLUSION

Patients found the touch screen easy to use, and were able to complete their history in the waiting area prior to consultation. They were universally happy to keep a printout of their history. The clinicians were able to spend more time discussing risks and treatment options, and were able to ask supplementary questions rather than repeatedly obtaining basic data. Printouts of the PDF were retained in the notes as part of the medical record. This technology has shown great potential in allowing more new patients to be seen, increasing efficiency in carrying out regular reviews, gathering better clinical information and reducing patient distress when asking sensitive questions.

Perceived benefits are - more rapid and thorough clinical assessment; semi-automated follow up; health screening; and patient surveys. There are applications for this technology in many fields of medical practice.

REFERENCES

SELF PROVIDED GUIDED MEDICAL HISTORY IS FAST, COMPLETE AND ACCURATE

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REFERENCES

Dried blood Spot Testing for Hepatitis B and C in the Chinese Community living in Northern Ireland

Annelies McCurley¹, Seana Murray¹, Neil McDougall²
Hepatitis B&C Managed Clinical Network¹, Regional Liver Unit², Royal Victoria Hospital, Belfast

Introduction
The epidemiology of hepatitis B and C is changing throughout Europe, with immigration cited by the European Centre for Disease Control and Prevention as the main reason (ECDC, 2014). Northern Ireland still has a very low prevalence of viral hepatitis, with an average of 80-100 HBV and 100-120 HCV cases being diagnosed every year. Certain groups however are at higher risk of infection including those born in high or intermediate endemic areas.

Aim
The aim was to set up a single viral hepatitis community screening event to offer testing to members of the Chinese community in Belfast in an effort to determine the prevalence of Hepatitis B (HBV) and Hepatitis C (HCV).

Methods
Members of the Belfast Chinese Community were invited to attend a Hepatitis B&C awareness and testing session held in the Chinese Welfare Centre. As part of the criterion only those individuals that were registered with a GP were eligible for screening. All those attending for testing were educated regarding the advantages and disadvantages of screening through a presentation (translated) and literature. Dry blood spot (DBS) testing was used as an alternative to venous sampling to try and encourage participation.

All patients (and their GPs) were informed of results by letter. Those with positive HBsAg or positive HCV antibody individuals were also contacted by telephone with the assistance of an interpreter and asked to attend a hospital clinic. Those who tested HBsAg negative and HBcAb positive were advised to attend their GP surgery for follow up HBV serology and HBV DNA. HIV testing was offered to all those with a positive result for either HBV or HCV.

Results
• Prior to the event, 97 individuals expressed an interest via telephone in attending the screening event. 19 of this cohort were not registered with a GP in Northern Ireland, and had to be excluded from the screening. A further 10 individuals who attended the session on the day were again excluded as they too were not registered with a GP giving a total of 29 individuals that were not eligible (figure 1). The final number of candidates included in the screening event was 55. A synopsis of the demographic is as follows: 62% female, 38% male, mean age 47, range 22-67.
• 13 (24%) individuals tested HBsAg negative and HBcAb positive, suggesting previous infection. Five (9%) individuals tested positive for chronic viral hepatitis – 4 were HBsAg positive and 1 was HCV PCR positive. All 5 subsequently attended a hepatology clinic for follow-up (figure 3).
• 43 (78%) of those presenting for testing reported they had never been vaccinated against HBV (figure 4).

Conclusion
DBS testing of a sample of the Chinese community living in a low prevalence area of the UK can detect chronic viral hepatitis in 9%. In addition, one third of those requesting screening were not registered with a GP and therefore could not be detected by current NHS services. This suggests that the NHS need to consider setting up screening services for ethnic communities even in low prevalence areas of the UK.

Conflict of interest
Funding for the dried blood spot testing kits and the analysis of these were paid for by Roche Pharmaceuticals.
GASTROENTEROLOGY SOLUTION DRIVES DEPARTMENTAL EFFICIENCY AND SUPPORTS PATIENT SELF-MANAGEMENT

University Hospital Southampton NHS Foundation Trust is expecting to achieve significant cost and time savings by implementing a new Ascribe gastroenterology system.

The gastroenterology department at Southampton sees around 4,000 Inflammatory Bowel Disease (IBD) patients. To meet new IBD quality standards as well as participate in the UK IBD registry and UK Biologics Audit, they required a system that would efficiently populate the audit databases, whilst providing clinicians with sufficient incentives to use the system and patients with more knowledge about their conditions to facilitate self-management.

Integrating clinical systems
Ascribe, part of EMIS Group, worked with the Southampton IBD team to develop a new integrated IBD solution. The trust uses several Ascribe clinical systems, including patient administration system (PAS), unscheduled care, and specialised clinical modules. As an integrated solution, clinicians have immediate access to all the investigations including relevant to managing the patient endoscopy, blood tests, histology, pathology and surgical history without leaving the IBD system in a meaningful format.

Facilitating supported self-management of care
A key objective was to improve patient self-management. Dr Fraser Cummings, consultant gastroenterologist and lead clinician for the project, said “there is a drive to improve patient knowledge about their conditions to help them self-manage their care. By enabling clinicians to record real-time data into one system, patients leave hospital fully informed about their conditions, which we hope will reduce health care resource utilization in the future.”

Reduced referrals and cost savings
The trust anticipates that they could save around £350,000 per annum using a management system for high cost drugs (anti-TNF biologic drugs), facilitating referral to research teams, and efficient use of nurse and administration time to run Virtual clinics and flare lines. Dr Cummings comments “clinicians and nurses have quicker and simpler access to accurate up to date patient data presented in a clinically meaningful way which saves significant time in the clinics as well as improving patient safety. Flare line activity is also recorded which means the reduction in emergency department referrals, further admissions and unnecessary clinic visits provided by this service can be captured and an accurate record of the contact recorded.”

Improved clinical engagement
Multi-disciplinary teams (MDT) now have one system and a single pathway for each patient in the IBD system, improving communication between the teams and fully recording all discussions regarding patient diagnosis or actions required. Dr Cummings comments “MDT scheduling and meeting screens are built into our Ascribe software to remove the need for separate spreadsheets and systems. Patient care is improved by ensuring all decisions are captured and available at any point for reference immediately after meetings.”

Comprehensive, accurate clinical procedure recording and reporting
Ascribe’s endoscopy solutions help clinicians improve their procedure recording and reporting capability. Based on national and professional standards, our solutions can help quickly and efficiently produce reports for standards that meet BSG Guidelines. By having a more informed record of patient procedures, we can help improve patient care and safety.

To find out more, please contact marketing@ascribe.com

“We expect to save at least £350,000 per year by improving correct drug use in gastroenterology”
FIT FOR THE FUTURE

Measurement of faecal haemoglobin concentration (f-Hb) is now well established in screening for significant colorectal neoplasia, that is, colorectal cancer and higher-risk adenoma. However, this is now moving to a quantitative faecal immunochemical test (FIT), rather than the traditional guaiac-based faecal occult blood test (gFOBT).

In February 2015 the Scottish government announced that it would be introducing a new bowel cancer test to simplify the sample collection process in a bid to increase participation in Scotland’s national bowel screening programme and save even more lives1. This new FIT screening test will see participants returning a small sample from just one bowel motion in a hygienic sample picker device, instead of the three samples on a test card as required for the current test. In addition to simplification for the user this FIT based assay ensures improved specificity and sensitivity and also offers great potential for managing the pathway of symptomatic patients.

Scotland has performed an evaluation of feasibility and clinical outcomes of FIT as a first-line test2 and a two-centre assessment is currently underway in England. Interestingly, most clinical guidelines still state that faecal tests should not be used in the assessment of symptomatic patients, but these recommendations apply to gFOBT, not to the very different and much better FIT. Evidence is rapidly accumulating that f-Hb is an excellent rule-out test for both colorectal neoplasia and inflammatory bowel disease (IBD) with very high Negative Predictive Values (NPV) using a low cut off of less than 10 µg of Hb/g of faeces.

At a meeting of the Colorectal Cancer Screening Committee, World Endoscopy Organization, held in Vienna in October 2014, there was much discussion on FIT in screening. However, the presentation that stimulated much interest was that of Professor Bob Steele from the University of Dundee. Professor Steele described the published pilot study done in Dundee on assessment of those with suspected colorectal disease using f-Hb3. This was performed to assess whether f-Hb could assist in rationalising referrals for colonoscopy, which have rapidly increased recently through the Be Clear on Cancer and Detect Cancer Early campaigns as well as through referrals from the screening programmes and subsequent surveillance needs. However, although lower abdominal symptoms are common, significant colorectal disease is not. He then described some concepts arising from a more extensive study, based on the novel but routine referral pathway existing in NHS Tayside, investigating the use of f-Hb AND faecal calprotectin in assessment of the symptomatic. He showed that, if a patient has undetectable f-Hb, significant colorectal disease is very unlikely. Using this rule-out strategy, although some cases of adenoma and IBD would be missed, 40% of urgent referrals for colonoscopy could be saved. Patient pathways using diagnostics in digestive health are changing. Quantitative f-Hb and calprotectin are now evidence-based tools to assess the symptomatic and rationalise referrals for colonoscopy: they should be adopted ubiquitously.

Alpha Laboratories (www.alphalabs.co.uk) has been a key supplier of faecal tests for haemoglobin and calprotectin for many years. In anticipation of the increasing clinical indications for FIT analyses, Alpha Laboratories has partnered with Kyowa Medex for provision of the HM-JACKarc automated quantitative FIT system to the Bowel Screening Programmes and for development in symptomatic testing. As per the progress made with the now NICE-approved calprotectin analyses, Alpha Laboratories is developing a similar approach with f-Hb measurements on HM-JACKarc.

References

After the success of the Digestive Disorders Federation 2012 conference, we are pleased to announce the 2nd Digestive Disorders Federation conference will take place 22 – 25 June 2015 in London ExCeL.

Five societies and Associations in the field of Digestive Disorders are joining together in a combined conference to replace their annual conferences in 2015:

- The Association of Coloproctology of Great Britain and Ireland (ACPGBI)
- Association of Upper Gastrointestinal Surgeons (AUGIS)
- British Association for Parenteral and Enteral Nutrition (BAPEN)
- British Association for the Study of the Liver (BASL)
- British Society of Gastroenterology (BSG)

This is a major four day international conference in the vibrant city of London.

**The first day:** Postgraduate education day & multi-disciplinary professional interaction. Suitable for Consultant CPD and Trainee Postgraduate education

**The main scientific programme (days 2-4):** Clinical and translational research symposia, clinical updates, state of the art lectures, moderated poster rounds covering topics in surgical and medical gastroenterology, nutrition and hepatology.

If you are a Hepatologist, Surgeon, Gastroenterologist, Non Clinical Scientist, Nurse, Dietician, GI Pharmacist, Nutrition Specialist or an Allied Health Professional in the field of Gastroenterology, you should not miss this exciting conference!

**Contact Details**

To contact the DDF Conference Secretariat MCI UK LTD, please contact: DDF2015@mci-group.com

If you are interested in Exhibition & Sponsorship Opportunities, please contact: DDF2015industry@mci-group.com

For further information on DDF 2015, please visit conference website: www.ddf2015.org.uk
Why You Should Consider Alternative EWD Chemistries

The alternative EWD chemistries project was started nearly two years ago. The Project partners were Audere Medical Services Ltd, Amity International, and the project leader was Peskett Solutions Ltd (Ruhof UK).

We are pleased to announce that the project was a resounding success and we are now in a position to offer our services to all hospitals using EWD's.

During the EWD project the following questions were raised:

**Will the Trust save money changing to alternative EWD Chemistries?**
- We have saved our project Hospital £56,000 per annum on their EWD detergent, disinfectant.

**Are there any other added benefits with using alternative chemistries?**
- Our alternative EWD project has been running for nearly two years. The customer has been monitoring the chemical effects to the EWD's and Endoscopes.
- The endoscope manufacturer has reported a 23% reduction in scope damage from the cleaning and disinfectant chemistries.
- The customer has reported an impressive increase of 41% up time. This has been contributed to the alternative chemistries and improved servicing and parts.

**How do you deal with Type Testing?**
- The type testing for the chemistries is performed by the validation company on site. The alternative chemistries were selected to chemically match the chemistries supplied by the EWD manufacturer. This decision was based on ensuring EWD and Endoscope compatibility.

**What about Patient safety?**
- To offer alternative chemistries we needed to ensure that all the required EWD validation testing was carried out to current relevant standards. The endoscopes over the last 2 years have shown no significant signs of deterioration. We are confident that this will continue and there should be no impact on Patient Safety.

Please contact Matthew to discuss the alternative EWD chemistries project further.
Tel: 01323 511038 Email: support@peskettsolutions.com