THESYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

Volume 17, 2018 Issue 05 ISSN number 2313-8084

Rheumatology & Heart Failure eLearning Modules

Clinical Implications of Bioinformatics

Meeting Reece Edmends

Developing an Agenda for Future Health Services Research in Malta

WELCOME TO OUR NEW HCP PORTAL

On **gskpro.com/en-mt/** you will find resources that will help you support your patients and practice:

ACCESS TOOLS FOR BETTER PATIENT COMPLIANCE

REGISTER TODAY
GSKPRO.COM/EN-MT/

MLT_GIB/OTH/0008/18a
Prepared: August 2018

AN ISLAND, BREXIT & A MOST PERFECT STORM

On 29 March 2017, the European Council received the notification by the UK of its intention to withdraw from the EU. This set in motion a chain of events within the pharmaceutical industry, amongst other things. Contingency plans by industry, academia and specific member states have kicked in with a view to address any foreseeable regulatory challenges, primarily medicine shortages together with any associated price hikes. An unexpected twist in the Brexit drama is the expected significant loss of 30% in the European Medicines Agency's workforce owing to its relocation to Amsterdam by 29 March 2019, when the United Kingdom withdraws from the EU. Although this may well mean a golden career opportunity for some, as from 1 August 2018 it has also resulted in a reduction of regulatory services offered by the Agency. Interestingly, the European Medicines Agency's lease of its London headquarters, 30 Churchill Place in Canary Wharf, does not expire until 2039 and there is no early break clause. It is understood that EMA pays around €14m each year for rent and has an outstanding liability for the remainder of the term of approximately €400m (including service charges).

As highlighted in a recent article, *Can Registration Procedures of Pharmaceuticals Inadvertently Contribute to Off-Label Prescribing in Children?*[1] published in 2016, one of the regulatory challenges faced by Malta is that a high number of medicine registrations rely on article 126(a) of Directive 2001/83/EC. Article 126a states that *"in the absence of a marketing authorisation or of a pending application for a medicinal product authorized in another Member State in accordance with this Directive, a Member State may for justified public health reasons authorise the placing on the market of the said medicinal product."* The authors found that as of 2016, 1877 out of 5025 medicines (37%) available on the Maltese market had a valid article 126a licence. Further to this, 1705 out of 5025 medicines (34%) authorized in Malta had a marketing authorization holder registered in the UK. In keeping with this, the Maltese Medicines Authority is currently advising suppliers to identify alternative source countries in the EU in lieu of the UK; repackaging of the medicinal product should be performed if the pack is not available in English/Maltese language. Obviously this could lead to rising costs of medicines because of any added costs for those UK-registered products which are retained on the local market, but also possibly due to decreased market competition for specific active ingredients following any UK registration cancellations.

In order for medicines to be imported and distributed within the EU, medicinal products need to be quality control-tested and released by a qualified person [QP] inside the EU [with the exception of products from Switzerland, where the testing done in Switzerland can be accepted; in this case you still need a QP release inside the EU]. Following Brexit, for those UK products remaining on our market, these will now need, as a minimum and assuming that the UK can negotiate an MRA similar to Switzerland's, an additional QP release inside the EU. Indeed, at least in the few months succeeding Brexit, this scenario can impact the access to UK medicines within the EU, including Malta, because of the additional quality control steps needed for release. Having said this, last August the UK Government officially reassured stakeholders that if there is a no-deal, the UK will continue to accept batch tests carried out in the EU, EEA countries and those third countries with which the EU has an MRA.

Further to this, Sanofi, AstraZeneca, Novo Nordisk, Novartis & MSD [as well as the UK's NHS] have stated that they will stockpile medicines for a number of weeks in preparation for a hard Brexit. This follows a call from EMA, the Association of the British Pharmaceutical Industry, and the BioIndustry Association who advocated preparedness for the possibility of an interruption in medication supplies. In keeping with this, one must also mention the fact that the perception that access to UK medicines may be affected, as well that their price may increase, could lead to a scenario where Maltese patients start to stockpile medicines sourced from the UK. It would be reassuring and appreciated if stakeholders within the pharma industry are continuously kept updated on the matter by local authorities in a timely manner to mitigate any shooting from the hip.

Ian Ellul

REFERENCE

1. Ellul I, Grech V, Attard-Montalto S. Can Registration Procedures of Pharmaceuticals Inadvertently Contribute to Off-Label Prescribing in Children? *Therapeutic Innovation & Regulatory Science* 2016;50(6): 808-816.

Editor-in-Chief: Dr Wilfred Galea
Managing Editor: Dr Ian C Ellul
Sales & circulation Director: Carmen Cachia

Email: mpl@thesynapse.net
Telephone: +356 21453973/4

Publisher:
Medical Portals Ltd
The Professional Services Centre
Guzi Cutajar Street, Dingli
Malta, Europe

Production: Outlook Coop

Printing: Europrint Ltd

OUR COLLABORATORS

The magazine is distributed free of charge to all Maltese doctors, pharmacists & dentists, as well as students of the aforementioned professions, with a print run of 3500 copies.

Annual subscription rates outside Malta: Six issues €90 or equivalent, worldwide

WITH ULTIBRO® BREEZHALER® EXACERBATION PREVENTION IS IN YOUR HANDS[1]

ULTIBRO® BREEZHALER® is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)[2]

FLAME STUDY RESULTS[1]

"...[ULTIBRO® BREEZHALER®] showed not only non-inferiority, but also... consistent superiority to [Seretide®* Accuhaler®] for all outcomes related to exacerbations, lung function† and health status**."[1†§]

The FLAME study is a 52-week head-to-head trial comparing ULTIBRO® BREEZHALER® with Seretide® Accuhaler® (LABA/ICS) in 3362 exacerbating‡ COPD patients.[1] The primary endpoint was to demonstrate that ULTIBRO® BREEZHALER® was at least non-inferior to Seretide® Accuhaler® in reduction of all exacerbations. Superiority over Seretide® Accuhaler® was a pre-defined secondary endpoint.[1]

*Fluticasone/salmeterol 500/50 mcg BID. †Lung function trough FEV$_1$ (P<0.001).[1] **Health-related quality of life, SGRQ-C (P<0.01).[1] ‡Patients had at least one moderate or severe exacerbation in the previous 12 months.[1] §Annual rate reduction of all exacerbations (mild/moderate/severe): ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 11% (RR 0.89, P=0.003). Annual rate reduction of moderate or severe exacerbations: ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 17% (RR 0.83, P<0.001). Annual rate reduction of severe exacerbations: ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 13% (RR 0.87, P=0.23).[1] Seretide® Accuhaler® is a registered trademark by GSK.

BID, twice daily; COPD, chronic obstructive pulmonary disease.

ONCE DAILY
ultibro® breezhaler®
indacaterol maleate/glycopyrronium bromide
inhalation powder

Ultibro Breezhaler inhalation powder, hard capsules

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Refer to section 4.8 of the SmPC for how to report adverse reactions.

PRESENTATION: medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Refer to section 4.8 of the SmPC for how to report adverse reactions. **INDICATIONS:** Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro Breezhaler inhaler. Ultibro Breezhaler is recommended to be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day. Ultibro Breezhaler can be used at the recommended dose in elderly patients (75 years of age and older). Ultibro Breezhaler can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis it should be used only if the expected benefit outweighs the potential risk. Ultibro Breezhaler can be used at the recommended dose in patients with mild and moderate hepatic impairment. There are no data available for the use of Ultibro Breezhaler in patients with severe hepatic impairment, therefore caution should be observed in these patients. There is no relevant use of Ultibro Breezhaler in the paediatric population (under 18 years) in the indication COPD. The safety and efficacy of Ultibro Breezhaler in children have not been established. No data are available Method of administration For inhalation use only. The capsules must not be swallowed. The capsules must be administered only using the Ultibro Breezhaler inhaler. The inhaler provided with each new prescription should be used.Patients should be instructed on how to administer the medicinal product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicinal product rather than inhaling it. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the other excipients. **WARNINGS/PRECAUTIONS:** Ultibro Breezhaler should not be administered concomitantly with medicinal products containing other long-acting beta-adrenergic agonists or long-acting muscarinic antagonists, the pharmacotherapeutic groups to which the components of Ultibro Breezhaler belong. ***Asthma:*** Ultibro Breezhaler should not be used for the treatment of asthma due to the absence of data in this indication. Long-acting beta2-adrenergic agonists may increase the risk of asthma-related serious adverse events, including asthma-related deaths, when used for the treatment of asthma. Not for acute use: Ultibro Breezhaler is not indicated for the treatment of acute episodes of bronchospasm. Hypersensitivity related to indacaterol or glycopyrronium. Immediate hypersensitivity reactions have been reported after administration of indacaterol, one of the components of Ultibro Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, treatment should be discontinued immediately and alternative therapy instituted. ***Paradoxical bronchospasm:*** Administration of Ultibro Breezhaler may result in paradoxical bronchospasm which can be life-threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted. *Narrow-angle glaucoma:* No data are available in patients with narrow-angle glaucoma, therefore Ultibro Breezhaler should be used with caution in these patients. Patients should be informed about the signs and symptoms of acute narrow-angle glaucoma and should be informed to stop using Ultibro Breezhaler should any of these signs or symptoms develop.*Urinary retention:* No data are available in patients with urinary retention, therefore Ultibro Breezhaler should be used with caution in these patients. Patients with severe renal impairment: These patients should be monitored closely for potential adverse reactions. ***Cardiovascular effects:*** Ultibro Breezhaler should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension). ***Hypokalaemia:*** Beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias. Clinically relevant effects of hypokalaemia have not been observed in clinical studies of Ultibro Breezhaler at the recommended therapeutic dose. ***Hyperglycaemia*** Inhalation of high doses of beta2-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Ultibro Breezhaler plasma glucose should be monitored more closely in diabetic patients. Ultibro Breezhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2-adrenergic agonists. ***Pregnancy and Lactation:*** There are no data from the use of Ultibro Breezhaler in pregnant women available. Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, Ultibro Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. The use of Ultibro Breezhaler by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. ***Excipients:*** This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. **INTERACTIONS:** Information on the potential for interactions is based on the potential for each of its two active substances. Beta-adrenergic blockers may weaken or antagonise the effect of beta$_2$-adrenergic agonists. Therefore, Ultibro Breezhaler should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution. The co-administration of Ultibro Breezhaler with other anticholinergic-containing medicinal products has not been studied and is therefore not recommended. Concomitant administration of other sympathomimetics(alone or as part of combination therapy) may potentiate the adverse events of indacaterol. Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or nonpotassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta$_2$-adrenergic agonists, therefore use with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-glycoprotein (P-gp), raises the systemic exposure of indacaterol up to two-fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended indacaterol dose. **ADVERSE REACTIONS:** The presentation of the safety profile is based on the experience with Ultibro Breezhaler and the individual active substances. Ultibro Breezhaler showed similar adverse reactions to the individual components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of these components may be expected in the combination. The most common adverse reactions with Ultibro Breezhaler are: Upper respiratory tract infections. Common: Pyrexia, chest pain, dyspepsia, dental caries, bladder obstruction and urinary retention, cough, oropharyngeal pain including throat irritation, dizziness, headache, nasopharyngitis, urinary tract infections, sinusitis, rhinitis, chest pain, hypersensitivity, diabetes mellitus and hyperglycaemia. Uncommon: Fatigue, peripheral oedema, muscle spasm, myalgia, pain extremity, dry mouth, pruritis, rash, glaucoma, myalgia, musculoskeletal pain, paradoxical bronchospasm, dysphonia, epistaxis, gastroenteritis, tachycardia, palpitations, insomnia. Please refer to SmPC for a full list of adverse events for Ultibro Breezhaler. **LEGAL CATEGORY:**POM **PACK SIZES:** Single pack containing 10x1 or 3x10 hard capsules, together with one inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBERS:** EU/1/13/862/003, EU/1/13/862/007 **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc. Representative Office Malta P.O Box 4, Marsa, MRS 1000 Malta. Tel: +35621222872

2018-MT-ULT-23-JUL-2018b

References

1. Wedzicha JA, *et al.* Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Engl J Med. 2016 Jun 9;374(23):2222-34.
2. Novartis Europharm Ltd. Ultibro Breezhaler Summary of product characteristics.

NOVARTIS

ULT Ad1 11/18 MT

AUTHORS

Dr Gianpaolo Tomaselli BA MA PhD currently works as a Research Support Officer at the University of Malta within the Department of Health Services Management (Faculty of Health Sciences). He holds a PhD in Economics and Management in Healthcare from University Magna Graecia of Catanzaro (Italy).His main research areas are corporate social responsibility and health management and policy. The co-authors are Prof. Sandra Buttigieg, Prof. Neville Calleja and Dr Kenneth Grech.

Dr Natasha Azzopardi Muscat MD (Melit) MSc (Melit) MSc (Lond) PhD (Maastricht) is the President of the European Public Health Association (EUPHA). She currently works as a consultant in public health medicine at the Directorate for Health Information and Research in Malta and as a Senior Lecturer within the Department of Health Services Management (University of Malta). Her research focuses on European Union health policy and small state health systems. The co-authors are Prof. Sandra Buttigieg, Prof. Neville Calleja and Dr Kenneth Grech.

Prof. Albert Cilia-Vincenti MD FRCPath is a surgical pathologist practicing privately. He is a former scientific delegate to the European Medicines Agency, pathology services director to the British and Maltese health services, and a former teacher of London and Malta Universities. He trained at London's Royal Marsden, Royal Free, St George's, Charing Cross and The Middlesex hospitals.

Dr Alfred Grech MD graduated from the University of Malta in 1985. He has been working in Primary Health (specifically at Paola Health Centre) for these last 30 years. His special interests are molecular biology and epigenetics. As a pastime he cultivates bonsai trees and plays his sax alto. The co-author of the article is Dr Michael Balzan.

Dr Pierre Vassallo MD PhD FACA Artz fur Radiologie specialised in radiology at the Institute of Clinical Radiology at the University of Muenster, Germany and the Memorial Sloan-Kettering Cancer Center, New York, US. He is currently Consultant Radiologist and Managing Director at DaVinci Health, Malta.

ISSUE GUIDE

TheSynapse

Actifed*

Actifed* oral solutions and tablets provide symptomatic relief of upper respiratory tract disorders [1-7]

Actifed* DM COUGH LINCTUS

- relieves dry cough and nasal congestion [3,6]

Actifed* SYRUP AND TABLETS

- clears blocked and runny noses [2,5]

Actifed* EXPECTORANT

- clears chesty cough and nasal congestion [4,7]

DOSAGE		
LIQUIDS	children aged 2 to 5 years [2-4]	2.5ml every 4-6hrs as required
	children aged 6 to 11 years [2-4]	5ml every 4-6hrs as required
	adults (including the elderly) and children aged 12 years and over [5-7]	10ml every 4-6hrs as required
TABLETS	adults (including the elderly) and children aged 12 years and over [1]	1 tablet every 4-6hrs as required

OTC legal status applies for oral solutions in adults and children aged 12 years and over.

ACTIFED ABRIDGED PRESCRIBING INFORMATION: *Please refer to full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAME:** ACTIFED**. ACTIVE INGREDIENT:** *Actifed DM Cough Linctus:* Each 5ml contains Dextromethorphan Hydrobromide 10mg, Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; *Actifed Syrup:* Each 5ml contains Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; *Actifed Expectorant:* Each 5ml contains Triprolidine Hydrochloride 1.25mg, Pseudoephedrine Hydrochloride 30mg and Guaiphenesin 100mg; *Actifed Tablets:* Each tablet contains Pseudoephedrine Hydrochloride 60mg; Triprolidine Hydrochloride 2.5mg**. PHARMACEUTICAL FORM:** Oral Solution and Tablets**. INDICATIONS:** Symptomatic relief of upper respiratory tract disorders which are benefited by a combination of: Actifed DM Linctus: a nasal decongestant, an anti-histamine and an antitussive; Actifed Syrup: a nasal decongestant, and an anti-histamine; Actifed Expectorant: a nasal decongestant, an anti-histamine and an expectorant; Actifed Tablets: a nasal decongestant, and an anti-histamine**. DOSAGE:** *please refer to full SPC. Actifed DM Cough Linctus, Actifed Syrup and Actifed Expectorant* are authorised for use without the need of a medical prescription in Adults and Children over 12 years**.** In Children between 2-11 years of age, these products are authorised for use only against a medical prescription as recommended by your doctor**. CONTRAINDICATIONS:** Previous intolerance to any of the active substances; use of MAOI's in the preceding two weeks; severe hypertension or heart disease; concomitant use of pseudoephedrine can cause a rise in blood pressure**. PRECAUTIONS:** May cause drowsiness; avoid the concomitant use of alcohol or other centrally active sedatives; use with caution in patients with liver impairment or moderate to severe renal impairment**. INTERACTIONS:** Sympathomimetics; MAOI's**. ADVERSE EVENTS:** Central nervous system depression or excitation with drowsiness being reported most frequently; sleep disturbance and rarely hallucinations have also been reported; skin rashes, tachycardia, dryness of mouth, nose and throat and urinary retention have occasionally been reported especially in men with prostatic enlargement**. PREGNANCY AND LACTATION:** Administration should only be considered if the expected benefits to the mother outweigh the potential risks to foetus or child**. PRESENTATION:** *DM Cough Linctus, Expectorant, Syrup:* Amber glass bottle x 100ml; Tablets: Pack x 24 tablets**.** Marketing Authorisation Holder: Glaxo Wellcome UK Limited, **Marketing Authorisation Number:** MA 167/00101-**7 Legal category:** POM – Actifed Tablets, POM – Actifed DM Cough Linctus, Actifed Syrup, Actifed Expectorant in Children between 2-11 years, OTC – Actifed DM Cough Linctus, Actifed Syrup, Actifed Expectorant in Adults and Children over 12 years**. For further information and full prescribing information contact GlaxoSmithKline (Malta)** Ltd: Tel**.** 21238131**. Date of preparation:** January 2015

In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd(Tel: +356 21238131)

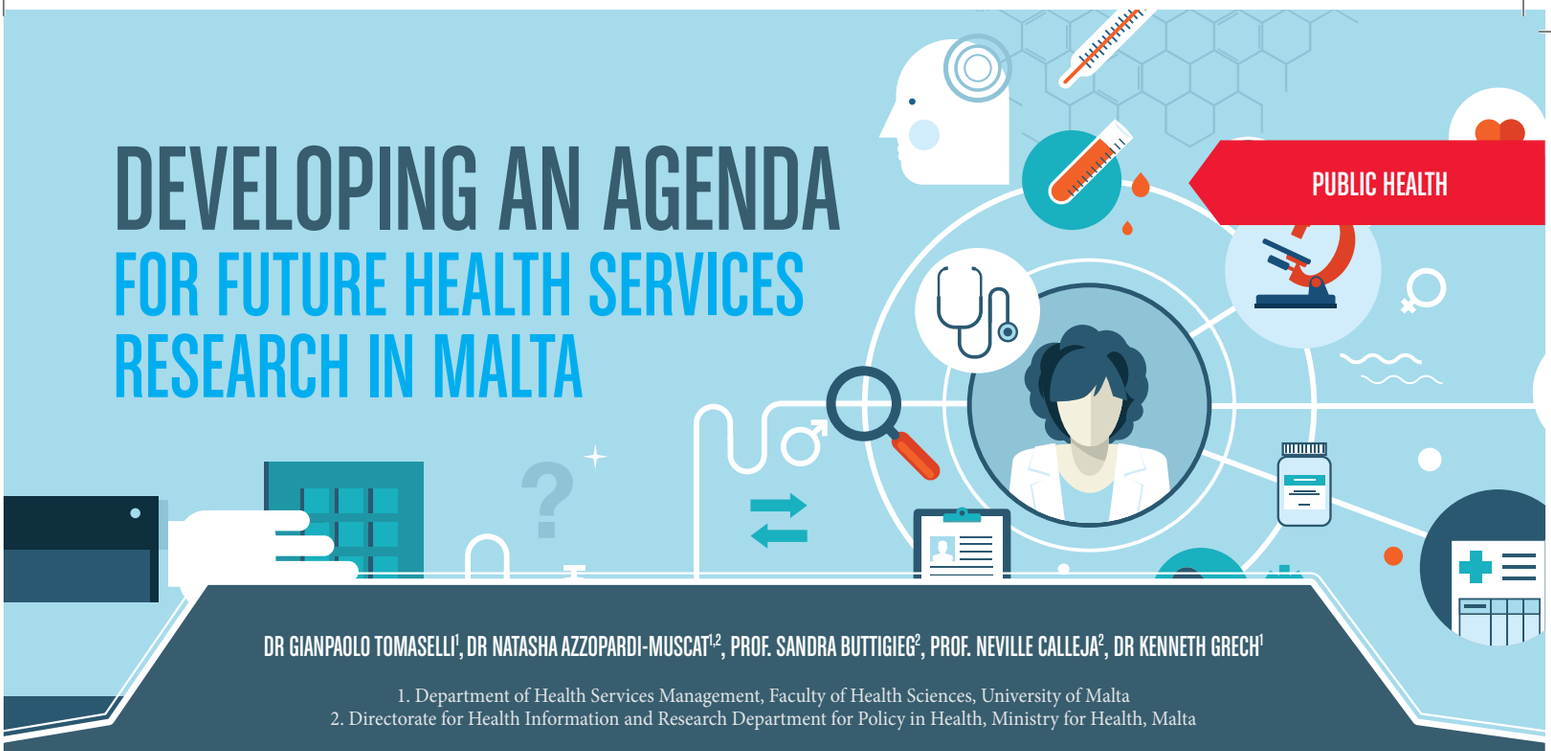
REPORTING ADVERSE EVENTS (AEs): **If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to:** GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131)

Alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system: Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

References: 1. Actifed Tablets SPC (Apr 2014); 2. Actifed Syrup SPC (Mar 2015); 3. Actifed DM Cough Linctus SPC (Jan 2015); 4. Actifed Expectorant SPC (Jan 2015); 5. Actifed Syrup SPC OTC (Mar 2015); 6. Actifed DM Cough Linctus SPC OTC (Jan 2015); 7. Actifed Expectorant SPC OTC (Jan 2015)

Job No: MLT_GIB/PDH/0005/16 Date of preparation: February 2016

DEVELOPING AN AGENDA FOR FUTURE HEALTH SERVICES RESEARCH IN MALTA



DR GIANPAOLO TOMASELLI[1], DR NATASHA AZZOPARDI-MUSCAT[1,2], PROF. SANDRA BUTTIGIEG[2], PROF. NEVILLE CALLEJA[2], DR KENNETH GRECH[1]

1. Department of Health Services Management, Faculty of Health Sciences, University of Malta
2. Directorate for Health Information and Research Department for Policy in Health, Ministry for Health, Malta

ABSTRACT

The Maltese health system is undergoing a period of change and transformation. This is partly in response to the changing socio-economic environment within the country. Planning and delivering adequate and appropriate health services necessitates that relevant local research on the health system takes place. In order to identify the top priorities for the Maltese health system, a National Round Table Consultation was organised by the Department of Health Services Management at the University of Malta and the Directorate for Health Information and Research on the 14 December 2017. This was conducted within the framework of the HORIZON 2020 EU project "Transfer of Organisational Innovations for Resilient, Effective, equitable, Accessible, Sustainable and Comprehensive Health Services and Systems (TO-REACH)", setting a future research agenda for health systems in which 28 partners from 20 countries are participating.

45 stakeholders from academia, the public service, private sector and NGOs attended and participated in the round table meeting. Reports from interactive workshops were collated and compiled into an overall report. Document analysis using a structured health systems analysis framework was carried out.

There was broad consensus on several priorities and challenges that health systems are facing today at both national and European levels. Access to health services and universal health coverage were identified as key research priorities. Furthermore, it was felt that particular attention should be devoted to research on health workforce planning and on the effects of the implementation of new technologies within health systems (including digital health and social media). Research on hospital leadership and governance within the changing health system context was also identified as important. Local stakeholders believe that better collaboration and networking between countries would be beneficial for the sustainability of the national health sector. As a way forward, knowledge gaps should be bridged through the collection/collation of evidence gathered through research conducted within the Maltese health system, leading to a more solid, efficient, evidence-based and responsive national health system.

BACKGROUND

Over the last decade, the Maltese health system has faced growing common challenges which include (among others) issues related to an aging population, as well as economic and financial pressures that motivate the pursuit of potential solutions for a more efficient, accessible, innovative and equitable healthcare. Although a strong political and public health leadership allowed Malta to make important improvements and advances to its health system over the last years, there are still problems that need to be addressed at the national level. According to the Hit Report published by the European Observatory on Health Systems and Policies (2017),[1] in Malta, there is the need to adapt the health system to an increasingly growing and diverse population, namely building capacity, allowing a more efficient distribution of scares resources, strengthening primary care and mental health, improving information systems, reducing access to medicine obstacles, and addressing challenges related to the sustainability of healthcare.[2,3]

To address the current challenges, there is a necessity for research evidence on our local health services, in order to identify and implement more effective and sustainable ways to organize, manage, finance, and deliver high quality care to persons living and working in Malta. For this purpose, a National Round Table Consultation meeting was held in Malta to obtain feedback from health stakeholders coming from different sectors and to identify most urgent challenges and priorities of the national health system, as well as gather suggestions to address the current issues.

METHODOLOGY

The Malta National Round Table Consultation on Health Services Research took place on 14 December 2017 at the Valletta Campus of the University of Malta. It was organised by the Department of Health Services Management within the University of Malta in collaboration with the Directorate for Health Information and Research within the Ministry for Health, as part of the HORIZON 2020 EU project "Transfer of

TABLE 1
HEALTH SYSTEMS PRIORITIES AT NATIONAL AND EUROPEAN LEVEL

	BROAD PRIORITY TOPICS	SUB-TOPICS	SPECIFIC FOCUS	LEVEL CONCERNED
ACADEMIA	Health integration and coordination	• Health systems challenges • Sociodemographic challenges • Profile of burden of disease	• Needs of future audience for: ageing population, migrants, DM screening, neurodegenerative diseases, diabetes and obesity • Integration of health and social care services; minimisation of fragmentation of care; improvement in efficiency and effectiveness of services • HR and clinical leadership development through capacity building • Person-centred care • Disinvestment agenda	National and EU
	Health promotion and prevention	• Health services gaps	• Healthy lifestyle promotion • Health education	
	Research	• Health services gaps	• The practical use of University research • Multi-sectoral government approach and interdisciplinary research • Strategy for communicating research priorities without being overwhelming • Patient participation in research	
	IT, innovation and use of data	• Health systems challenges • Health services gaps	• Joint procurement of medicines/services/technologies • Digital health & social media • Misinformation	
	European integration	• Health services gaps	• European collaboration in research	
	Empowerment and health democracy	• Health systems challenges • Sociodemographic challenges	• Feminisation of the health service • Gender-issues	
PUBLIC SECTOR	Health integration and coordination	• Health systems challenges • Sociodemographic challenges	• Obesity, including in children, population ageing, migrants, mental health, diabetes, sexual health, oncology, cardiovascular diseases • Decentralisation from secondary to primary care • Prioritising health requirements • KPIs for hospitals • Patient safety and quality of care • Disinvestment agenda • Primary care gaps • Inter-sectoral collaboration	National and EU
	Health promotion and prevention	• Health services gaps	• Sexual health education (health promotion and prevention) • Employees wellbeing • Improving employees' skills • Health prevention	
	Research	• Health services gaps	• Evidence-based practice • Citizen expectations and market research • Strategy for communicating research priorities • Interdisciplinary collaboration in academia • Knowledge transfer - private to public and vice-versa	
	IT, innovation and use of data	• Health systems challenges • Health services gaps	• Data availability and accessibility • New technologies • Joint procurement of medicines/services/technologies • Insufficient use of existing health data	
	European integration	• Health services gaps	• European Reference Networks	
	Empowerment and health democracy	• Health systems challenges • Sociodemographic challenges • Profile of burden of disease	• Bridging inequalities • Skills to meet needs and address gaps • Housing poverty • Needs of minority groups (migrants, men who have sex with men, etc.)	

Organisational innovations for Resilient, Effective, equitable, Accessible, Sustainable and Comprehensive Health Services and Systems (TO-REACH)".

45 stakeholders from different backgrounds (namely academia, the public service, private sector and NGOs) participated and they were divided into three working groups and asked to propose and discuss a list for health services research priorities at both a national and EU level.

During the discussion, the following questions were addressed by participants: i) Which are the most important priorities for health systems research within Malta and which challenges will they help to address?; ii) What are the research priorities/projects for which we see added value in organising health systems research at a European level? iii) Which are the key criteria that need to be satisfied to ensure effective and appropriate transfer of innovation between health systems in different countries?

PRIVATE SECTOR	Health integration and coordination	• Health systems challenges • Sociodemographic challenges • Health services gaps	• Improving employees' skills • Disinvestment agenda • Person-centred care • Delays of care • Duplication of services • Accountability	National and EU
	Health promotion and prevention	• Health services gaps	• To prepare new parents for their new role • Personal wellbeing education • Mental and emotional health • Population ageing, diabetes, obesity, mental and emotional health • Social determinants of health	
	Research	• Health services gaps	• Training of healthcare staff - evidence-based research on training to render it effective and efficient • Knowledge transfer - private to public and vice-versa • Citizen expectations and market research • Cancer research • To create exchange possibility with foreign research groups • Strategy for communicating research priorities • The practical use of University research • Evaluation of research	
	IT, innovation and use of data	• Health systems challenges • Health services gaps	• Digital health • Data management • To create public-private network to share information solutions	
	Empowerment and health democracy	• Sociodemographic challenges • Profile of burden of disease	• Decrease health inequalities • Decrease barriers to accessibility • Person-centred care • Family wellbeing	
NGOS	Healthcare pathway, integration and coordination	• Health systems challenges • Sociodemographic challenges • Health services gaps	• Availability of medicines and ability to include new medicines in publicly funded formularies • Mental health, patient safety, migration, poverty studies, tobacco consumption • Role of NGOs in Health systems challenges • Inter-sectoral collaboration • Improving employees' skills • Health expenditure • Implementation science in healthcare • Capacity building • Quality of care • Prioritising health requirements	National
	Communication and use of data	Health services gaps	• Lack of data on medications usage • E-Health	

Reports from the interactive workshops were collected and compiled into an overall report. Document analysis using a structured health systems analysis framework[4] was carried out. Data were further processed and analysed with the support of NVivo 11 Software.

RESULTS

Table 1 illustrates the results from the discussion workshop on research priorities and challenges that need to be addressed by the Maltese health system at both national and European level. The initial results presented here arise from a thematic analysis of the discussions that took place within stakeholders from different sectors (academia, public sector, private sector, and NGOs).

CONCLUSION

The priorities listed in Table 1 suggest that easier access to funds, workforce mobility among health professionals, collaboration and networking between EU countries, and industry involvement in health research are the main expectations from a future programme of organised Health System Research both at national and EU level. Moreover, access to health services and healthcare coverage deserves particular importance specifically with regards to marginalised and minority groups of the population. The role of new technologies and digital health was perceived as a fundamental asset, which needs to be further developed in order to provide innovative solutions, considering the rapid and continuous technology advances.

The main challenges and priorities of the Maltese health system are related to health integration and coordination, intersectoral collaboration, health promotion and prevention, health education, research implementation, innovation, IT and digital health implementation, data management, European integration, empowerment, and health democracy.

The Maltese national health system, as well as other European health systems, should take into account the priority issues that emerged from this workshop so as to spearhead improvement of the health services sector. The aim is to attain more efficient, equitable, responsive and sustainable health systems, as well as to strengthen gaps and weaknesses within the service delivery.

ABOUT THE TO-REACH PROJECT

The To-reach project is financed by the EU Horizon 2020 programme. The project's multidisciplinary consortium includes 28 partners from 20 countries including EU member states, Norway, Canada, Israel and the US, and it covers research funders, policymakers and the research community. Its main goal is to prepare a joint European research programme aimed at producing research evidence supporting healthcare services and systems to become more resilient, effective, equitable, accessible, sustainable and comprehensive. Thus, To-reach is focused on setting out clearly what needs to be done in terms of the future Health Services and Systems Research agenda, with the objectives of: i) identifying common challenges and organizational needs across Europe; ii) proposing possible solutions to improve health systems performance; and iii) identifying the most effective ways to organize, manage, finance, and deliver high quality, sustainable, and equitable care to citizens.

Details of the To-reach initiative are available at https://to-reach.eu/ and https://twitter.com/toreachEU.

ACKNOWLEDGEMENTS

The authors would like to thank all people involved in the organisation of the National Round Table Consultation held on the 14 December 2017 and all participants. We also thank rapporteurs who have collected feedback from stakeholders presented in this paper.

REFERENCES

1. Azzopardi-Muscat N, Buttigieg S, Calleja N, Merkur S. Malta: Health system review. *Health Systems in Transition* 2017;19(1):1–137. Available from: http://www.euro.who.int/__data/assets/pdf_file/0009/332883/Malta-Hit.pdf?ua=1
2. European Commission. 2018 European Semester: Assessment of progress on structural reforms, prevention and correction of macroeconomic imbalances, and results of in-depth reviews under Regulation (EU) No 1176/2011. Country report Malta 2018. Available from: https://ec.europa.eu/info/sites/info/files/2018-european-semester-country-report-malta-en.pdf
3. European Commission. State of Health in the EU. Malta Country Health Profile 2017. Available from: https://ec.europa.eu/health/sites/health/files/state/docs/chp_malta_english.pdf
4. World Health Organisation. Everybody's business: Strengthening health systems to improve health outcomes. WHO's framework for action. Geneva. 2007. Available from: http://www.who.int/healthsystems/strategy/everybodys_business.pdf

Dr Michelle (k/a Mikhaila) **Muscat** is a medical doctor in chemical pathology with extensive experience in clinical biochemistry. She is the creator and lead of 'Unraveling Chemical Pathology-UCP', which aims at promoting interest and understanding of chemical pathology-related topics, as well as organising other related activities.

Dr Muscat holds many relevant postgraduate degrees, including a postgraduate diploma, an MSc which was awarded with distinction, a PhD, and passed both the MRCS and FRCPath examinations. She has worked in hospitals in both Malta and the UK. She taught clinical biochemistry to medical students at the University of Malta between 2012 and 2107 and gave a guest lecture in Ireland this April to an MSc in Clinical Chemistry class. In 2017 she won the Furness Prize for Science Communication organised by The Royal College of Pathologists of England for sustained excellence in science communication. This was the first instance where a Maltese doctor was awarded this UK science communication prize.

How does your choice of ICS/LABA stand up to a 24-hour world?

Throughout day and night, their **24-hour world** needs an ICS/LABA that lasts. Relvar is the only ICS/LABA providing 24 hours of continuous efficacy from just one daily inhalation,[1] and is superior to ICS/LABAs in helping more patients improve asthma control in everyday clinical practice.*[2]

Relvar 92/22mcg & 184/22mcg are indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate:
- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta$_2$-agonists.
- patients already adequately controlled on both inhaled corticosteroid and long-acting beta$_2$-agonist.[3]

Please refer to full SmPC for detailed information.

ZINC Code: MLT_GIB/FFT/0005/18 Date of preparation: April 2018

Relvar Ellipta was developed in collaboration with INNOVIVA

RELVAR ELLIPTA
fluticasone furoate/vilanterol

References: 1. Bernstein DI, Bateman ED, Woodcock A, Toler WT, Forth R, Jacques L, *et al*. Fluticasone furoate (FF)/ vilanterol (100/25mcg or 200/25mcg) or FF (100mcg) in persistent asthma. *J Asthma* 2015;52(10):1073–1083. **2.** Woodcock A, Vestbo J, Bakerly ND, New J, Gibson JM, McCorkindale S, *et al*. Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open label, parallel group, randomised controlled trial. *Lancet* 2017; doi.org/10.1016/S0140-6736(17)32397-8. **3.** Relvar SmPC, March 2018.

RELVAR ELLIPTA ABRIDGED PRESCRIBING INFORMATION

Please refer to full Summary of Product Characteristics (SPC) before prescribing
TRADE NAME: Relvar Ellipta. **ACTIVE INGREDIENT:** *92mcg/22mcg dose*: 92mcg fluticasone furoate, 22mcg vilanterol (as trifenatate). *184mcg/22mcg dose*: 184mcg fluticasone furoate / 22mcg vilanterol (as trifenatate). **PHARMACEUTICAL FORM:** Inhalation powder, pre-dispensed. **INDICATIONS:** ***Asthma*** *(92/22mcg dose & 184/22mcg dose):* Regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate: patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta$_2$-agonists and patients already adequately controlled on both inhaled corticosteroid and long-acting beta$_2$-agonist. **COPD** (92/22mcg dose): For symptomatic treatment of adults with COPD with a FEV$_1$<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. **POSOLOGY:** *For Asthma*: One inhalation, once daily. *For COPD*: One inhalation of 92/22mcg dose, once daily. 184/22mcg is not indicated for patients with COPD. Relvar Ellipta should be administered at the same time of day, each day. *Refer to full SPC for full dosage recommendations.* **CONTRAINDICATIONS:** Hypersensitivity to active ingredients / excipients. **PRECAUTIONS:** Should not be used to treat acute asthma symptoms or acute exacerbation in COPD; Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing; Caution for use in severe cardiovascular disease or heart rhythm abnormalities, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium; Moderate to severe hepatic impairment: 92/22mcg dose should be used and patients should be monitored for systemic corticosteroid-related adverse reactions; Systemic corticosteroid effects may occur, particularly at high doses for long periods. Caution in patients with pulmonary tuberculosis or chronic or untreated infections; Blurred vision or other visual disturbances: referral to ophthalmologist for evaluation should be considered; Caution in diabetic patients; Physicians should remain vigilant for possible development of pneumonia in patients with COPD (clinical features overlap); Incidence of pneumonia in asthma common at higher dose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this product. **PREGNANCY/FERTILITY/LACTATION:** *Pregnancy:* only if expected benefit to mother outweighs risk to foetus. *Lactation:* consider benefit of breast feeding child and benefit of therapy for woman. *Fertility:* No data. **UNDESIRABLE EFFECTS:** *Very common (≥1/10):* headache, nasopharyngitis. *Common (≥1/100 & <1/10):* pneumonia, upper respiratory tract infetion, bronchitis, influenza, candiasis of mouth and throat. Oropharyngeal pain, Sinusitis, Pharyngitis, Rhinitis, Cough, Dysphonia, Abdominal pain, Arthralgia, Back pain, Fractures, Muscle spasms, pyrexia. *Refer to the SPC for full list of undesirable effects.* **LOCAL PRESENTATION:** Inhaler x 30 doses. **MARKETING AUTHORISATION NUMBER:** EU/1/13/886/001-6. **MARKETING AUTHORISATION HOLDER:** Glaxo Group Limited. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** March 2018.
In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131).

REPORTING ADVERSE EVENTS (AEs):
If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malta) Ltd, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131)
Malta: alternatively, any suspected AEs and medication errors can be reported via the Medicines Authority Adverse Drug Reactions reporting website: www.medicinesauthority.gov.mt/adrportal
Gibraltar: alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): https://yellowcard.mhra.gov.uk/

SHORT ACCOUNTS OF INTERESTING CASES, SOME MEDICAL DISASTERS, INVOLVING PATHOLOGY AND CLINICAL PRACTICE, FROM THE RECOLLECTION OF PROF. ALBERT CILIA-VINCENTI.

THE PITFALLS OF IMMUNOHISTOCHEMISTRY

This is 1996. I had returned to a consultant histopathologist's post at St Luke's Hospital the year before, and had become acquainted socially with a Maltese commercial lawyer and his ex-pat wife. Shortly afterwards, he informed me that his wife hasn't been well and that Dr Mario Vassallo had just performed a private gastroscopy, was worried she had something serious and whether I would mind looking at the biopsy material. Mario Vassallo found a large gastric ulcer with rolled edges, practically diagnostic of a carcinoma. Fortunately the histology showed a low grade lymphoma of "mucosa-associated lymphoid tissue" (MALT) type, which carried a far better prognosis.

The biology of MALT lymphoma had been worked out by Peter Isaacson in Dennis Wright's histopathology department in Southampton. He had also elucidated the intestinal high grade T-cell lymphomas that might complicate gluten sensitivity, although he had originally described them as intestinal histiocytic lymphomas before better immunohistochemical cellular diagnostic markers became available. Both these lines of research eventually led Peter Isaacson to the chair of pathology at University College Hospital in London and to the highest accolade in British science – Fellow of the Royal Society.

Professor Isaacson had also found that some low grade gastric MALT lymphomas regressed and totally resolved with anti-Helicobacter antibiotic therapy, but this course of therapy had no effect on the large gastric lesion Dr Vassallo was dealing with. The patient's husband asked me for the histological slides as they were visiting their daughter, a medical intern at the Memorial Sloan Kettering, New York's premier cancer hospital, where they would seek an oncology opinion.

On their return, the husband informed me that New York had not agreed with my diagnosis of low grade MALT lymphoma and had recommended a total gastrectomy and systemic chemotherapy. When he showed me their pathology report, I realised that in spite of the innumerable immunohistochemical stains they had performed, they issued two reports, one diagnosing a chronic peptic ulcer and the other a high grade lymphoma. They had returned the slides and paraffin block and I sent them to Professor Dennis Wright in Southampton who, like Peter Isaacson, was a lymphoma pathologist of world repute. He phoned me to ask, "what's the problem with this low grade MALT lymphoma?" He couldn't believe New York's interpretation of the pathology and the drastic treatment recommended. An oncologist from the Memorial subsequently phoned the husband to apologise for the mistake.

I phoned Professor Michael Whitehouse, oncologist at Southampton for guidance on treatment and he only recommended a six-month low dose course of chlorambucil. Her gastric lesion melted away and Mario Vassallo followed her up. More than 20 years later she's remained disease-free.

TheSynapse eLearning Module

RHEUMATOLOGY

Dr Michela Frendo

EARLY REFERRAL OF RHEUMATIC MUSCULOSKELETAL DISEASE - WHY?

LEARNING OBJECTIVES

- To recognise and appreciate the burden of rheumatic and musculoskeletal diseases which are often underestimated
- To understand the importance of early referral and diagnosis of rheumatic conditions since early diagnosis equates to better quality of life and improved outcomes
- To develop a structured approach to diagnosis and understand the importance of history and clinical examination
- To understand the importance of a multidisciplinary approach to rheumatic conditions and the role of the family doctor as a key player in the team

Dr Bernard Coleiro

RAYNAUD'S PHENOMENON

LEARNING OBJECTIVES

- To recognise and diagnose Raynaud's Phenomenon
- To differentiate between Primary and Secondary Raynaud's Phenomenon
- To counsel and treat patients with Raynaud's Phenomenon
- To appreciate when it is appropriate to refer patients with Raynaud's Phenomenon to a Specialist Centre

Dr Cecilia Mercieca

JUVENILE IDIOPATHIC ARTHRITIS

LEARNING OBJECTIVES

- To explain differential diagnosis and improve recognition of distinctive clinical features of JIA
- To increase awareness on the different clinical patterns of the condition
- To emphasize the importance of performing appropriate investigations
- To increase familiarisation with management and with the special considerations which need to be considered when managing young people with JIA

Prof Andrew Borg

DISENTANGLING FIBROMYALGIA

LEARNING OBJECTIVES

- To improve understanding of Fibromyalgia, including diagnosis, symptoms and the relationship between the condition, sleep disturbances and anxiety
- To discuss management options; both pharmacological and non-pharmacological including EULAR recommendations
- To increase appreciation of the importance of a multidisciplinary support structure in the pro-active management of patients affected by the condition

DON'T DELAY CONNECT TODAY

Arthritis and Rheumatism Association Malta

THIS E-LEARNING MODULE INSPIRED BY THE EULAR CAMPAIGN *"DON'T DELAY, CONNECT TODAY"* AND MADE POSSIBLE BY ASSOCIATION OF ARTHRITIS AND RHEUMATISM MALTA (ARAM).

ONLINE ON-DEMAND TRAINING COURSE SUPPORTED BY

This project has been funded by the Small Initiatives Support Scheme (SIS), managed by the Malta Council for the Voluntary Sector (MCVS). This project reflects the views only of the author, and the MCVS cannot be held responsible for the content or any use which may be made of the information contained therein."

FOCUS ON

CLINICAL IMPLICATIONS OF BIOINFORMATICS

DR ALFRED GRECH & DR MICHAEL BALZAN

ABSTRACT

Over the past decade, the science of clinical bioinformatics has become one of the fastest growing areas of research and development within the healthcare environment. Indeed, the job of a bioinformatician has become an integral part of research laboratories. In particular, clinical bioinformatics aims to address the challenges in diagnosis, prognosis, and therapies of patients with diseases such as cancer, neurodegenerative (e.g. ALS, Alzheimer's and Parkinson's disease), allergic (e.g. asthma), and psychiatric disorders (e.g. depression), amongst others.

INTRODUCTION

In 1970, Ben Hesper and Paulien Hogeweg coined the term bioinformatics to refer to "the study of information processes in biotic systems". In consequence, bioinformatics was placed as a field parallel to biochemistry and biophysics.[1] Since then, the digital world expanded and the definition of bioinformatics took on a whole new meaning. It now combines the fields of biology, computer science, engineering, mathematics, and statistics to decipher biological data and make sense of it in translational research.

Over the past decade, the advent of high throughput or next generation sequencing (NGS) has accelerated the rate at which genes and co-regulated gene networks are discovered. Indeed, a vast amount of data is now available, in particular from the completion of the human genome project in 2003. Together, this data is being used to modulate disease outcome, predisposition, and progression.[2] For this reason, the science of clinical bioinformatics has become one of the fastest growing areas of development within the healthcare environment. It is an important component in laboratories that generate and interpret data from molecular genetics testing. Overall, the aim of clinical bioinformatics is to address the challenges in initial diagnosis, prognosis, and therapies of patients[3] with diseases such as cancer, neurodegenerative and psychiatric disorders, amongst others.

CANCER

In clinical medicine, it has become apparent that there is a need to develop and introduce advanced and new bioinformatics methodologies to answer the specific question of cancer.[4] In order for cancer bioinformatics to be effective, the tools must thus concentrate on the communication, metabolism, proliferation, and signalling of the disease. In particular, cancer bioinformatics is expected to have a significant role in the identification and validation of biomarkers. For example, one of the strategies is to evaluate and monitor biomarkers at different stages and time points during cancer development. Identified as dynamic network biomarkers, these markers should compare with clinical informatics, such as patient complaints, history, symptoms, and therapies. In addition, these biomarkers should also correlate to biochemical analyses, imaging profiles, pathologies, physician's examinations, and other measurements.[5]

For instance, through a genetic screen of hepatic cellular carcinoma, Sawey *et al.*[6] discovered that a common alteration in liver cancer (11q13.3 amplification) causes the activation of the fibroblast growth factor 19 (FGF19), a hormone that regulates bile production with effects on glucose and lipid metabolism. In turn, through subsequent bioinformatics analysis with mouse models and RNAi, it was found that activation of FGF19 results in selective responsiveness to FGF19 inhibition. Therefore, Sawey *et al.* propose for the 11q13.3 amplification to be used as a biomarker for patients who, in all likelihood, will respond to anti-FGF19 therapies. In a somewhat similar approach, Baert-Desurmont *et al.*[7] revealed that a combination of single nucleotide polymorphisms (8q23, 15q13 and 18q21 SNPs) could explain an increased risk for colorectal cancer.

Using genome-wide screening methods, aberrant expression profiles of microRNAs (miRNAs) have also been identified in human cancers, thus revealing their potential as diagnostic and prognostic biomarkers of cancer.[8] Now, in order to infer the regulatory processes of miRNAs, bioinformatics approaches are fundamental. For example, Laczny *et al.*[9] developed a comprehensive and integrative tool, called miRTrail, to generate reliable and robust data on deregulated pathogenic processes which could offer insights into the interactions between genes

and miRNAs. In fact, the use of miRTrail on melanoma samples demonstrated how this platform opened new avenues for investigating a wide range of diseases, including cancer.

In clinical practice and medical research, medical image processing facilitates the accurate, initial detection and diagnosis of cancer. Indeed, medical imaging - imaging in clinical pathology, nuclear magnetic resonance imaging, positron emission tomography, and ultrasonic computed tomography - is one of the most important factors in the application of cancer bioinformatics. Kimori *et al.*[10] for instance, used a mathematical morphology-based approach to enhance fine features of a lesion with high suppression of surrounding tissues. Here, the effectiveness of the method was evaluated in terms of the contrast improvement ratio as applied to three kinds of medical images: a chest radiographic image, a mammographic image, and a retinal image.

Overall, the aim of cancer bioinformatics is to continue developing tools so that the right treatment is provided to the right patient at the right time, based on the characteristics of each patient's tumour; in other words, tailored bioinformatics.

NEURODEGENERATIVE DISEASES

It is known that the economical and societal costs of neurodegenerative diseases are accelerating. Therefore, there is a demand to find new solutions to resolve the situation.[11] However, having said that, progress in this area has proved to be challenging. In part, this is because the cause of diseases such as Alzheimer's (AD) or Parkinson's disease (PD) is not known, making them difficult to understand.[12] In addition, while understanding these diseases on a molecular level could lead to the development of better biomarkers and treatments, the enormous amount of data involved renders it an arduous task. For this reason, bioinformatics approaches are used to manage data from high-throughput technologies, pushing forward the frontiers of this field.

In regard to late onset AD and PD, both have an obvious genetic component, however, their genetic architecture is complex, with just a few, constant, associated risk factors. It is therefore possible that undiscovered AD and PD-related genes exist. Kim *et al.*[13] using biomedical text mining, were able to pinpoint genes that have a direct relationship with both neurodegenerative diseases. In another approach, Hofmann-Apitius *et al.*[12] developed a bioinformatics and modelling method based on patient data available to the public. Here, the work presented was driven through AETIONOMY, a public-private partnership between the European Union and the pharmaceutical industry association EFPIA.

ALS, short for amyotrophic lateral sclerosis, is another neurodegenerative disease, but one that affects nerve cells in the brain and the spinal cord. To date, there is a vast volume of data capturing this motor neurone disease. In consequence, there is a corresponding need for storage and interpretation. In keeping with this, Abel *et al.*[14] presented an ALS online bioinformatics database (ALSoD) combining genotype, phenotype, and geographical information with associated analysis tools. Likewise, PRO-MINE (PROtein Mutations In NEurodegeneration)[15] is a database describing all TDP-43 disease mutations identified up to now; TDP-43 is a multifunctional RNA-binding protein found in AD, ALS, and also frontotemporal lobar degeneration.

ALLERGIC AND PSYCHIATRIC DISORDERS

In 2008, TIME magazine named 23andMe the invention of the year. 23andMe provides a home-based saliva collection kit that decodes the genomic DNA of adults and interprets their genetic health risks, with results accessible online. In particular, it tests for ten diseases, including AD, PD, and some rare blood diseases. It is important to note that the 23andMe kit describes if an individual has a higher risk of developing a disease but it is not intended to diagnose disease. It is meant to provide information that can be used to inform life decisions.

Using the 23andMe gene pool, Hyde *et al.*[16] discovered 15 genetic loci associated with a risk of major depression in people of European descent. In a similar approach, genome-wide analyses for personality traits identified 6 loci with correlations to psychiatric disorders.[17] In addition, through a multi-trait analysis of a genome-wide association study, Turley *et al.*[18] identified loci for depressive symptoms, neuroticism, and subjective well-being. Using this 23andMe gene pool, scientists have also discovered that asthma, eczema and hay fever share a genetic origin, in part due to shared genetic risk variants that dysregulate the expression of immune-related genes.[19]

CONCLUSION

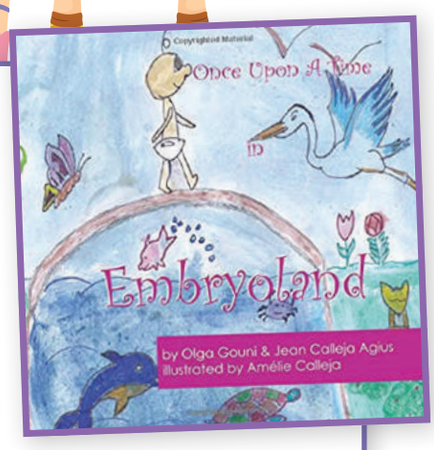
Overall, clinical bioinformatics is the critical step to discovering and developing new diagnostics and therapies for diseases. Here, we described cancer, neurodegenerative and psychiatric disorders, however, bioinformatics has been used in other disorders as well, such as acute rejection after renal transplantation[20] and lung diseases.[21] In addition, bioinformatics has been used in studies of model organisms such as *Saccharomyces cerevisiae* (yeast), *Drosophila melanogaster* (flies), and *Mus musculus* (mice), which in turn shed light onto non-model organisms such as humans.

It is evident that bioinformatics will continue to push the boundaries of medicine and shape clinical testing for the future. Just like microscopes, computers have become a requirement, and the job of a bioinformatician is now an integral part of research laboratories and also in the clinical setting. In the future, success will depend on improved analytics, annotations, software to deliver this information, and systems to capture the realised knowledge.[22]

REFERENCES

1. Hogeweg P. The roots of bioinformatics in theoretical biology. *PLoS Comput Biol* 2011; 7(3):e1002021.
2. Guffanti A, Simchovitz A, Soreq H. Emerging Bioinformatics Approaches for Analysis of NGS-Derived Coding and Non-Coding RNAs in Neurodegenerative Diseases. Front Cell Neurosci 2014; 8:89.
3. Wang X, Liotta L. Bioinformatics: A New Emerging Science. *Journal of Clinical Bioinformatics* 2011; 1(1):1.
4. Wu D, Rice CM, Wang X. Cancer Bioinformatics: A New Approach to Systems Clinical Medicine. *BMC Bioinformatics* 2012; 13:71.
5. Wang X. Role of Clinical Bioinformatics in the Development of Network-Based Biomarkers. *Journal of Clinical Bioinformatics* 2011; 1:28.

6. Sawey ET, Chanrion M, Cai C, *et al.* Identification of a Therapeutic Strategy Targeting Amplified FGF19 in Liver Cancer by Oncogenomic Screening. *Cancer Cell* 2011; 19(3):347-58.
7. Baert-Desurmont S, Charbonnier F, Houivet E, *et al.* Clinical Relevance of 8q23, 15q13 and 18q21 SNP Genotyping to Evaluate Colorectal Cancer Risk. Eur J Hum Genet 2016; 24:99-105.
8. Lan H, Lu H, Wang X, Jin H. MicroRNAs as Potential Biomarkers in Cancer: Opportunities and Challenges. Biomed Res Int 2015; 2015:125094.
9. Laczny C, Leidinger P, Haas J, *et al.* miRTrail - a Comprehensive Webserver for Analyzing Gene and miRNA Patterns to Enhance the Understanding of Regulatory Mechanisms in Diseases. *BMC Bioinformatics* 2012; 13:36.
10. Kimori Y. Mathematical Morphology-Based Approach to the Enhancement of Morphological Features in Medical Images. *J Clin Bioinforma* 2011; 1:33.
11. Paananen J. Bioinformatics in the Identification of Novel Targets and Pathways in Neurodegenerative Diseases. *Current Genetic Medicine Reports* 2017; 5:15-21.
12. Hofmann-Apitius M, Ball G, Gebel S, *et al.* Bioinformatics Mining and Modeling Methods for the Identification of Disease Mechanisms in Neurodegenerative Disorders. Int J Mol Sci 2015; 16(12):29179-206.
13. Kim YH, Beak SH, Charidimou A, Song M. Discovering New Genes in the Pathways of Common Sporadic Neurodegenerative Diseases: A Bioinformatics Approach. J Alzheimers Dis 2016; 51(1):293-312.
14. Abel O, Powell JF, Andersen PM, Al-Chalabi A. ALSoD: A User-Friendly Online Bioinformatics Tool for Amyotrophic Lateral Sclerosis Genetics. Hum Mutat 2012; 33(9):1345-51.
15. Pinto S, Vlahovicek K, Buratti E. PRO-MINE: A Bioinformatics Repository and Analytical Tool for TARDBP Mutations. Hum Mutat 2011; 32(1):E1948-58.
16. Hyde CL, Nagle MW, Tian C, *et al.* Identification of 15 Genetic Loci Associated with Risk of Major Depression in Individuals of European Descent. Nat Genet 2016; 48(9):1031-6.
17. Lo M-T, Hinds DA, Tung JY *et al.* Genome-Wide Analyses for Personality Traits Identify Six Genomic Loci and Show Correlations with Psychiatric Disorders. *Nat Genet* 2017; 49(1):152–156.
18. Turley P, Walters RK, Maghzian O, *et al.* Multi-Trait Analysis of Genome-Wide Association Summary Statistics Using MTAG. Nat Genet 2018; 50(2):229-237.
19. Ferreira MA, Vonk JM, Baurecht H, *et al.* Shared Genetic Origin of Asthma, Hay Fever and Eczema Elucidates Allergic Disease Biology. Nat Genet 2017; 49(12):1752-1757.
20. Wu D, Zhu D, Xu M, *et al.* Analysis of Transcriptional Factors and Regulation Networks in Patients with Acute Renal Allograft Rejection. J Proteome Res 2011; 7;10(1):175-81.
21. Chen H, Song Z, Qian M, Bai C, Wang X. Selection of Disease-Specific Biomarkers by Integrating Inflammatory Mediators with Clinical Informatics in AECOPD Patients: A Preliminary Study. J Cell Mol Med 2012; 16(6):1286-97.
22. Oliver GR, Hart SN, Klee EW. Bioinformatics for Clinical Next Generation Sequencing. Clin Chem 2015; 61(1):124-35.



ONCE UPON A TIME IN EMBRYOLAND

Olga Gouni (Author, Editor) | **Jean Calleja Agius** (Author) | **Amelie Calleja** (Illustrations)
Price: €22 | **Published:** On Amazon's CreateSpace Independent Publishing Platform in 2018

BLURB

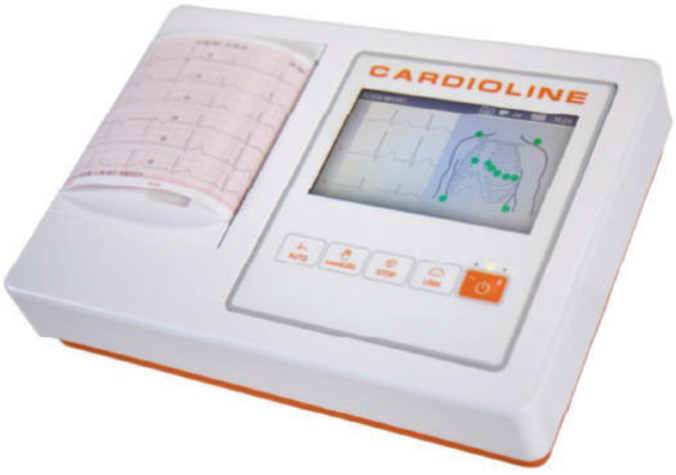
The journey in Embryoland is truly an amazing odyssey. And, this beautifully illustrated narrative offers readers, young or old, an incredibly imaginative journey to their own beginnings. Biology informs us about the researched scientific system of facts as to what happens for a new little body coming to life. The authors and the artist have managed to create a vibrant living vision of every human being conceived, grown, developed and matured over the nine months before being born. The intricate fascinating science of embryology is explained through this story recounted by the child herself as she is musing and dreaming about her own beginnings. This book has been written for any child, parent, educator or healthcare professional, who wishes to understand the journey from conception to birth. While adhering to accurate scientific facts based upon the advice of Prof. Jean Calleja Agius from the Department of Anatomy, Faculty of Medicine and Surgery at the University of Malta, the story itself has been written by the prenatal psychologist Olga Gouni from Cosmoanelixis Academy in Athens, Greece, and embellished by numerous illustrations by a child, Amelie, based on her understanding of the concepts of embryology. There is also a section at the end for activities and games related to embryology. This book has been 'conceived' as part of the COST Action ISI405: Building Intrapartum Research Through Health - an interdisciplinary whole system approach to understanding and contextualising physiological labour and birth (BIRTH) , and is intended to disseminate knowledge related to human conception, embryo development and birth to the general public, including children!

Blurb reproduced tale quale, as received by Prof. Jean Calleja Agius. Book available from: www.amazon.co.uk

JAMESCO
Trading Company Limited

A smarter approach to your health & wellbeing

CARDIOLINE ECG 100L



The ECG100L is a 12-lead 6 channel fully diagnostic electrocardiograph which displays, acquires, prints and stores ECG tracings for your patients.

It features a 5" colour touchscreen display, from which all operations can be easily performed. A smart user interface guides the user through the different steps necessary to acquire the electrocardiogram. Various messages on the screen inform the user of the ongoing operations and warn him in case of errors (for example in case of lead fail).

The ECG EasyApp has been designed to easily allow you to handle a patient ECGs.

Features:

- 5 " Color Touch Screen
- 12-Lead 6 Channel ECG
- 5-pin Patient Cable
- Sensitivity: 5, 10, 20 mm / mV
- 4 writing speeds: 5, 10, 25, 50 mm / s
- 50 ECG memory locations
- Battery or mains operated
- Printing formats: Standard or Cabrera 3, 3+1, 3+3 or 6 channels in automatic mode and 3 or 6 channels rhythm strip printing
- 100 mm wide paper roll
- Dimensions (mm): L 285 x W 204 x H 65
- Weight: approx 1.85 kg

SPECIAL INTRODUCTORY OFFER
STARTING FROM €1099
(NORMAL PRICE € 1416)

For more information kindly contact us on 21314333 or
info@jamescotrading.com

ALKAPTONURIA
FROM BENCH TO BEDSIDE - AND BEYOND

Dr Michelle Muscat meets MR REECE EDMENDS, the Administration and Communications officer of the Alkaptonuria Society based in Cambridge, UK.

Alkaptonuria is also known as black bone disease, a disorder affecting the metabolism of tyrosine and phenylalanine, where homogentistic acid accumulation occurs in connective tissue (ochronosis). In the young the disease may be asymptomatic, with the main finding being urinary discoloration when left standing with symptoms such as joint pains starting to develop as they grow older. In alkaptonuria there is homogentistic acid oxidase deficiency. The Egyptian mummy Harwa - believed to date back as far as 1500 BC - was actually documented to be ochronotic and probably had alkaptonuria. Alkaptonuria is an autosomal recessive disorder first described by the British doctor Sir Archibald Garrod in 1902 - interestingly, Sir Archibald served in Malta providing medical consultancy to the army during World War One and was made Knight Commander (KCMG).

WHAT ARE THE ORIGINS OF THE ALKAPTONURIA SOCIETY?

The AKU Society was founded in 2003 by Robert Gregory, a patient at the Royal Liverpool University Hospital, and his doctor, Professor Lakshimarayan Ranganath. After both his sons were diagnosed with alkaptonuria, social entrepreneur Nick Sireau also threw himself into the search for a treatment, becoming CEO in 2010 and hiring our first member of staff. Sireau left in 2015 but returned to the charity in 2017. He now leads a team of four staff and is assisted by a six-strong board of trustees, including Professor Ranganath. Sadly, Robert Gregory passed away in 2014. The NHS-funded Robert Gregory National Alkaptonuria Centre, established in Liverpool, is named in his honour.

DO YOU BELIEVE THE AWARENESS OF ALKAPTONURIA HAS CHANGED ALONG THE YEARS?

Sir Archibald Garrod's discovery of alkaptonuria in 1902 was a landmark in medical history. His definition of an inherited disease, attributed to 'inborn errors of metabolism', was an inspiration for modern genetics. For the next hundred years, however, there was little progress. Most patients were misdiagnosed. Even those diagnosed were told that they had to accustom themselves to a life of crippling pain. Only in the early 2000s did research begin into finding a treatment. Scientists at the National Institutes of Health in Maryland, US, ran clinical trials on nitisinone, which had already been licensed for use in hereditary tyrosinaemia type 1. The trials failed due to, among other things, recruitment difficulties, but those patients who were treated reported that they felt better. This inspired us to support research on nitisinone back in the UK.

WHAT WAS YOUR MOST REWARDING ACHIEVEMENT?

In 2012 we managed to persuade the NHS to establish and fund a dedicated National Alkaptonuria Centre at the Royal Liverpool University Hospital. This provides assessments and treatment for all adults with alkaptonuria in the UK. Patients attend for one week each year, getting expert care and off-label access to nitisinone. Since 2012, the centre has gone from strength to strength. It now serves over 60 patients, up from 21 in its first year. The effect of this on patients' lives is enormous.

CAN YOU ELABORATE ON THE EVENTS WHICH YOU ORGANISE? DO YOU SECURE FUNDING? HOW THE ASSOCIATION IS INVOLVED IN RESEARCH?

Each year, we organise at least two patient workshops. These allow patients to meet each other, to get updated on the latest research, and to get advice on how to manage their condition: diet, gait analysis and pain management are particularly popular topics. So far, we have organised seven workshops for adult British patients, two workshops for international patients, and one for children at the London Zoo. The events are free to attend and would not be possible without our community fundraisers and the generosity of private charitable trusts. We also organise an annual academic conference for researchers and clinicians to discuss advances in the field.

We are also the driving force behind the **DevelopAKUre** international clinical trials into nitisinone, which we believe treats alkaptonuria. In 2012, we put together a multi-national consortium which won a grant of six million euros (and seven million euros in co-financing) from the European Commission's FP7 programme. The trials, which are being carried out in Britain, France and Slovakia, are now at their final stage and will finish next year. If the results are good, we will apply for a marketing authorisation with the European Medicines Agency.

From left, Reece Edmends, Nick Sireau, and Ciarán Scott [clinical trials officer] at the EURORDIS European Conference on Rare Diseases and Orphan Products in Vienna 2018

The AKU Society recruited all the patients on the trials, and currently provides logistical support for patients at the UK's clinical site. We advertise the research at international conferences like the European Conference on Rare Diseases and Orphan Products. Pharmaceutical companies are impressed by our retention rate of 91%.

CAN YOU TELL US MORE ABOUT POSSIBLE MEDICAL ADVANCEMENTS ON THE HORIZON YOU ARE PERSONALLY EXCITED ABOUT?

Nitisinone, a synthetic reversible inhibitor of 4-hydroxyphenylpyruvate dioxygenase, is very effective in reducing homogentisic acid levels in the blood and (we hope) is of great clinical benefit. But it is not a perfect treatment. By blocking tyrosine metabolism, it causes an elevation in plasma tyrosine. In some patients, this hypertyrosinaemia leads to unpleasant side-effects – corneal keratopathy and skin irritation. As a result, we would like in the future to develop a nitisinone co-therapy with tyrosine ammonia lyase (TAL). We propose to use oral administration of this enzyme to selectively degrade tyrosine in the gut, lowering tyrosine absorption and preventing tyrosinaemia.

We would also like to test a gene therapy in mice that can be translated to AKU patients. The method and delivery will be part of a personalized medicine strategy that can overcome point mutations not only in AKU but also in many inherited metabolic diseases.

WHAT DO YOU ENVISAGE IN THE FUTURE FOR THE ALKAPTONURIA SOCIETY?

After the **DevelopAKUre** trials finish in 2019 where we hope to obtain a marketing authorisation from the European Medicines Agency, our remit should change significantly. Hopefully we will no longer have to invest so much energy into clinical research proving that nitisinone works. Instead, we could focus on optimising access to treatment. In the developing world, thousands of people currently suffer from AKU without any support. We are looking for funding to launch promotional campaigns in India and the Middle East over the coming years. More information may be found on www.akusociety.org

Nick Sireau receiving the Global Health Repurposing Award from Cures within Reach 2016

MR REECE EDMENDS

I READ THE SYNAPSE BECAUSE...

This is the first time I encountered the publication which is an innovative and interesting way of providing healthcare professionals with information, including the e-Learning service. I hope we can collaborate further in the near future.

ACTIVATE THE HEART*

ACTIVATE LIFE[1,2]

GUIDELINE† CLASS I RECOMMENDED[3,4]

Change your symptomatic HFrEF patients to ENTRESTO®

- **Activates the heart's beneficial response** by enhancing the natriuretic peptide system, while maintaining RAAS inhibition[5,6]
- **20% reduced risk** of CV death or first heart failure hospitalisation vs enalapril ($P<0.0001$; ARR=4.7%)[5‡]
- **Significant improvements in Quality of Life** vs enalapril, as measured by reduced deterioration of heart failure symptoms and physical limitations ($P=0.001$)[7§]

When you see symptoms, IT'S TIME FOR ENTRESTO[5]

Entresto®
sacubitril/valsartan

ARR = absolute risk reduction; CV = cardiovascular; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; RAAS = renin-angiotensin-aldosterone system.

*The complementary cardiovascular benefits of ENTRESTO in patients with HFrEF are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by sacubitril and the simultaneous inhibition of the deleterious effects of angiotensin II by valsartan.

†Based on 2016 ESC HF Guidelines and 2017 ACC/AHA/HFSA Guideline Update.

‡Primary end point.

§Secondary end point that measured the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ).

ENTRESTO™ ▼(sacubitril/valsartan) Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex). **Indications:** In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. **Dosage & administration:** The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3 - 4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy. **Warnings/Precautions:** Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Entresto must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with Entresto is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of Entresto. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing product. Hypotension: Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with Entresto during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). Blood pressure should be monitored routinely when initiating or during dose titration with Entresto. If hypotension occurs, temporary down-titration or discontinuation of Entresto is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m2). There is no experience in patients with end-stage renal disease and use of Entresto is not recommended. Use of Entresto may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. Entresto is not recommended in patients with end-stage renal disease. Hyperkalaemia: Entresto should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation of Entresto. If serum potassium level is >5.4 mmol/l discontinuation should be considered. **Angioedema:** Angioedema has been reported with Entresto. If angioedema occurs, discontinue Entresto immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. Entresto must not be re administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with Entresto because it is a neprilysin substrate. **Interactions:** Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Should not be coadministered with another ARB. Use with caution when co-administering Entresto with statins or PDE5 inhibitors. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered. Monitoring serum potassium is recommended if Entresto is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on Entresto who are taking NSAIDs concomitantly. Interactions between Entresto and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of Entresto and furosemide reduced Cmax and AUC of furosemide by 50% and28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and Entresto was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of Entresto with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin; ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of Entresto with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with Entresto in patients receiving metformin, the clinical status of the patient should be evaluated. **Fertility, pregnancy and lactation:** The use of Entresto is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether Entresto is excreted in human milk, but components were excreted in the milk of rats. Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue Entresto while breast feeding, taking into account the importance of Entresto to the mother. **Undesirable effects:** Very common (≥1/10): Hyperkalaemia, hypotension, renal impairment. Common (≥1/100 to <1/10): Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. Uncommon (≥1/1,000 to <1/100): Hypersensitivity, postural dizziness, pruritis, rash, angioedema. **Packs sizes:** Entresto 24 mg/26 mg – x28 tablets; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets. **Legal classification:** POM. Marketing **Authorisation Holder:** Novartis Europharm Ltd, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **Marketing Authorisation Numbers:** Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007. **Please refer to the Summary of Product Characteristics (SmPC) before prescribing.** Full Prescribing Information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872. 2018-MT-ENT-30-APR-2018

References: 1. Fala L. Entresto (sacubitril/valsartan): first-in-class angiotensin receptor neprilysin inhibitor FDA approved for patients with heart failure. *Am Health Drug Benefits*. 2015;8(6):330-334. 2. Volpe M, Carnovali M, Mastromarino V. The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. *Clin Sci*. 2016;130(2): 57-77. 3. Ponikowski P, Voors A, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37(27):2129-2200. 4. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017; 136(6):e137-e161. Epub 2017 Apr 28[1]. 5. ENTRESTO Core Data Sheet, version 1.1. Novartis Pharmaceuticals, August 2015. 6. McMurray JJV, Packer M, Desai AS, et al. Dual Angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure. *Eur J Heart Fail*. 2013;15(9):1062-1073. 7. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004.

NOVARTIS

your Way THESYNAPSE eLEARNING

GET YOUR ACCREDITATION

eLearning Module on *Heart Failure*

6 VIDEOS WITH ACADEMIC ACCREDITATION FROM

Medical Association of Malta — *0.5 Credits / video*

Malta College of Family Doctors — *0.5 Credits / video*

LEADING SPECIALISTS

Directly addressing 6 key topics involved in Diagnosis, Monitoring, Treatment and Complications that directly deal with Heart Failure.

CHALLENGE YOURSELF

With MCQ's following each video!

CLINICAL PRESENTATION
Dr Herbert Felice

INVESTIGATIONS
Dr Alex Borg

TREATMENT GUIDELINES
Dr Alice Moore

PHARMACOLOGIC APPROACH
Dr Robert G. Xuereb

CARDIAC AND NON-CARDIAC CO-MORBIDITIES
Dr Robert G. Xuereb, Prof. Emanuel Farrugia

HOW I MANAGE HEART FAILURE - GP PERSPECTIVE
Dr Alice Moore, Dr Silvio Grixti, Ms Janet Caruana

ONLINE ON-DEMAND TRAINING COURSE SUPPORTED BY

NOVARTIS

Keep It Pumping™

HF Ad1 11/18 MT

MANAGEMENT OF LOCALISED RENAL CELL CANCER

DR PIERRE VASSALLO

Renal cell cancer (RCC) is common, and its incidence is increasing due to increasing exposure to risk factors which include tobacco use, hypertension and obesity. Localised renal cancers are often detected incidentally, and their increased incidence also results from the increased use of imaging. Localised renal cancer now accounts for 60-70% of new RCC cases. Many of these cancers are slow growing and show little tendency to metastasize.

Only a minority of patients with localised renal cell cancer have any clinical signs such as haematuria or abdominal pain. These tumours are often detected incidentally on ultrasound but are best characterised using computed tomography (CT), where they may appear as a solid contrast-enhancing mass or a complex cystic lesion. Imaging features are similar on Magnetic Resonance Imaging (MRI) and the latter is equally accurate for the evaluation of renal lesions; it may be used in patients who are allergic to iodinated contrast material, in those with poor renal function, in lesions containing complex haemorrhage or where radiation exposure must be avoided (e.g. pregnancy).

Localised renal cancer is defined as a stage I or II tumor that remains confined within the renal capsule (Fig 1). Since renal cancers may be cystic, it is important to identify those features in cystic lesions which point towards malignant disease. In 1986, Morton Bozniak suggested a classification of cystic lesions based on CT findings to help standardise their management (Fig 2). This cyst classification system has since then become widely accepted and is used to guide treatment decisions. Bosniak Type III and IV lesions are very likely malignant and require further management.

Management options for localised renal cancer include radical nephrectomy, partial nephrectomy, thermal ablation and active observation. The choice of treatment is individualised based on patient age and co-morbidities, tumor characteristics and renal function considerations. A significant proportion of localised RCCs are indolent and slow growing; they can therefore be managed by nephron-sparing treatments (partial nephrectomy or thermal ablation) or even through active observation. The new American Urological Association (AUA) 2017 guidelines recommend a change in strategy with a decreased use of radical nephrectomy and an increased use of imaging-guided renal biopsy, thermal ablation and active observation.

Radical nephrectomy is the preferred treatment in patients with aggressive tumor types, for larger tumours that show complex or infiltrative imaging features (Fig 3 and 4) and when normal contralateral renal function is present.

Partial nephrectomy or tumour enucleation can be considered in tumours <4cm in diameter (Fig 5). These should also be considered in patients with an anatomical or functional solitary kidney, for bilateral or multifocal tumours, for patients with familial renal cell cancer, for young patients, and for those with limited renal function or with comorbidities that could lead to deterioration in renal function. In otherwise healthy individuals who present with a lesion that shows aggressive imaging features, a partial nephrectomy or enucleation is recommended without prior biopsy.

Imaging-guided tumour biopsy provides a means of confirming the diagnosis of malignancy and establishing the tumour subtype (and consequently the degree of aggressiveness of the tumour). In the past, it was claimed that percutaneous biopsy was associated with an increased risk of tumor seeding

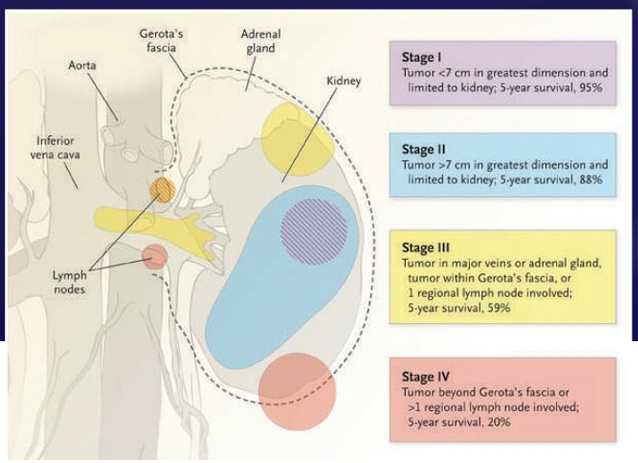


Figure 1. Renal cancer staging: Stage I and II lesions are considered local renal cancers as they do not extend beyond the renal capsule. Source: http://www.aboutcancer.com/renal_cell_stage_survival_nejm.jpeg

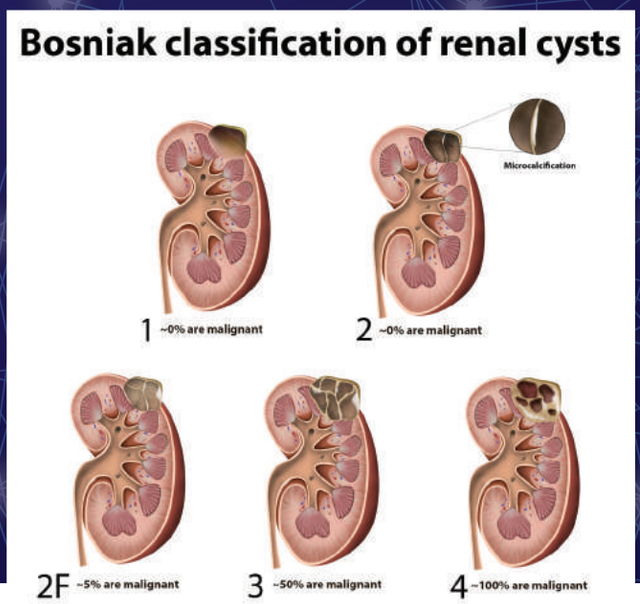


Figure 2. Bozniak classification of renal cysts: *Type 1* refers to a unilocular thin-walled cyst with no enhancement. A *type 2* cyst contains thin non-enhancing septa and may show thin calcifications. Hyperdense (haemorrhagic) cysts measuring <3cm in diameter are also considered type 2 lesions. Hyperdense cysts ≥3cm and those with minimal septal nodularity and minimal enhancement are considered *type 2F* (F indicates need for follow-up). Cysts with thick nodular enhancing septa (*Type 3*) and those with solid enhancing proliferations (*Type 4*) are considered malignant and require management.

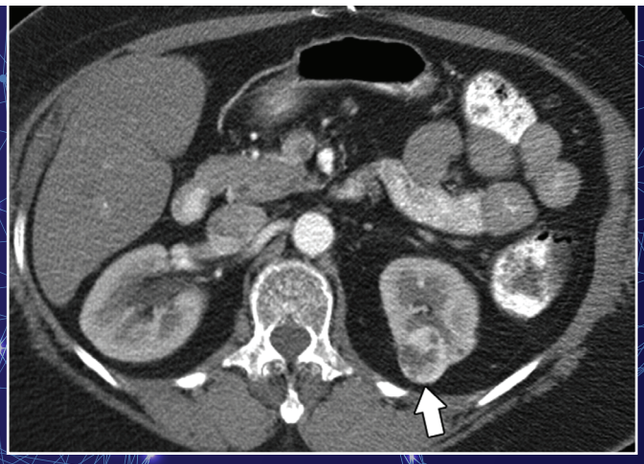


Figure 3. Contrast-enhanced CT scan showing a complex enhancing tumour (arrow) in the lower pole of the left kidney. No hilar, vascular or lymph node involvement is evident.

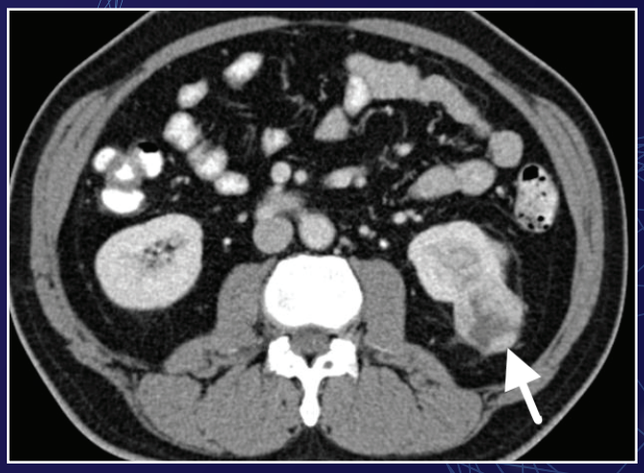
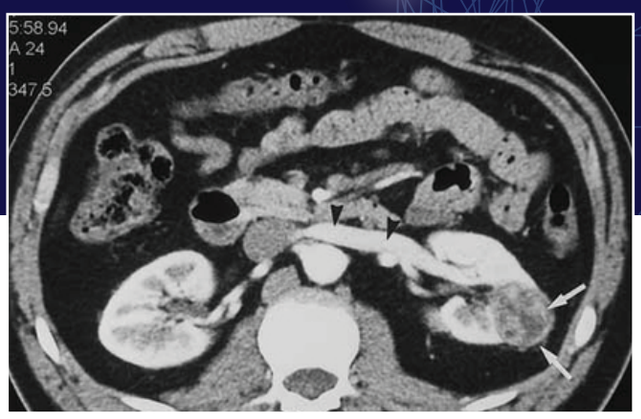


Figure 4. CT Scan Bosniak type IV cystic lesion (arrow) showing thick enhancing walls. Minimal perinephric fat stranding is also present.

along the biopsy tract. However, this is now known to be exceedingly rare particularly when using a coaxial technique; this technique allows multiple samples to be obtained and thermal ablation to be performed through a single tract.

Thermal ablation can be a considered treatment option when nephron-sparing is a priority and in patients who are unfit for surgery. In patients who are frail, who suffer from multiple co-morbidities or who refuse surgical intervention, and who have aggressive-looking lesions, biopsy and ablation may be performed in the same sitting. Tumour ablation is used for Stage 1 tumours and obtains most reliable results in tumours <3cm in diameter (Fig 6). Radiofrequency ablation or cryoablation may be implemented under imaging or laparoscopic guidance. Imaging guidance is more efficient



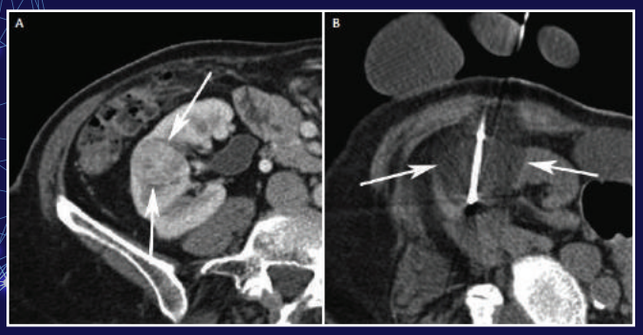


Figure 6. CT scans showing a T1 tumor (arrows in A and B) in the lower pole of the right kidney. Image B shows a radiofrequency ablative probe place centrally within the lesion inserted under CT guidance.

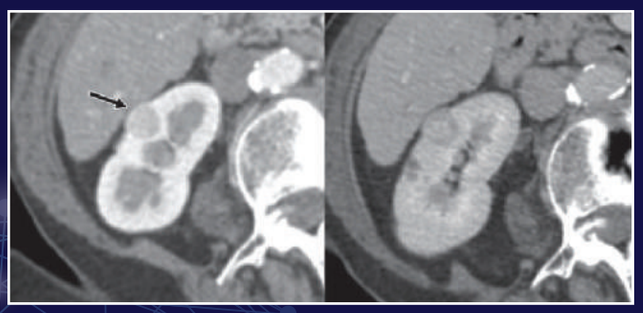


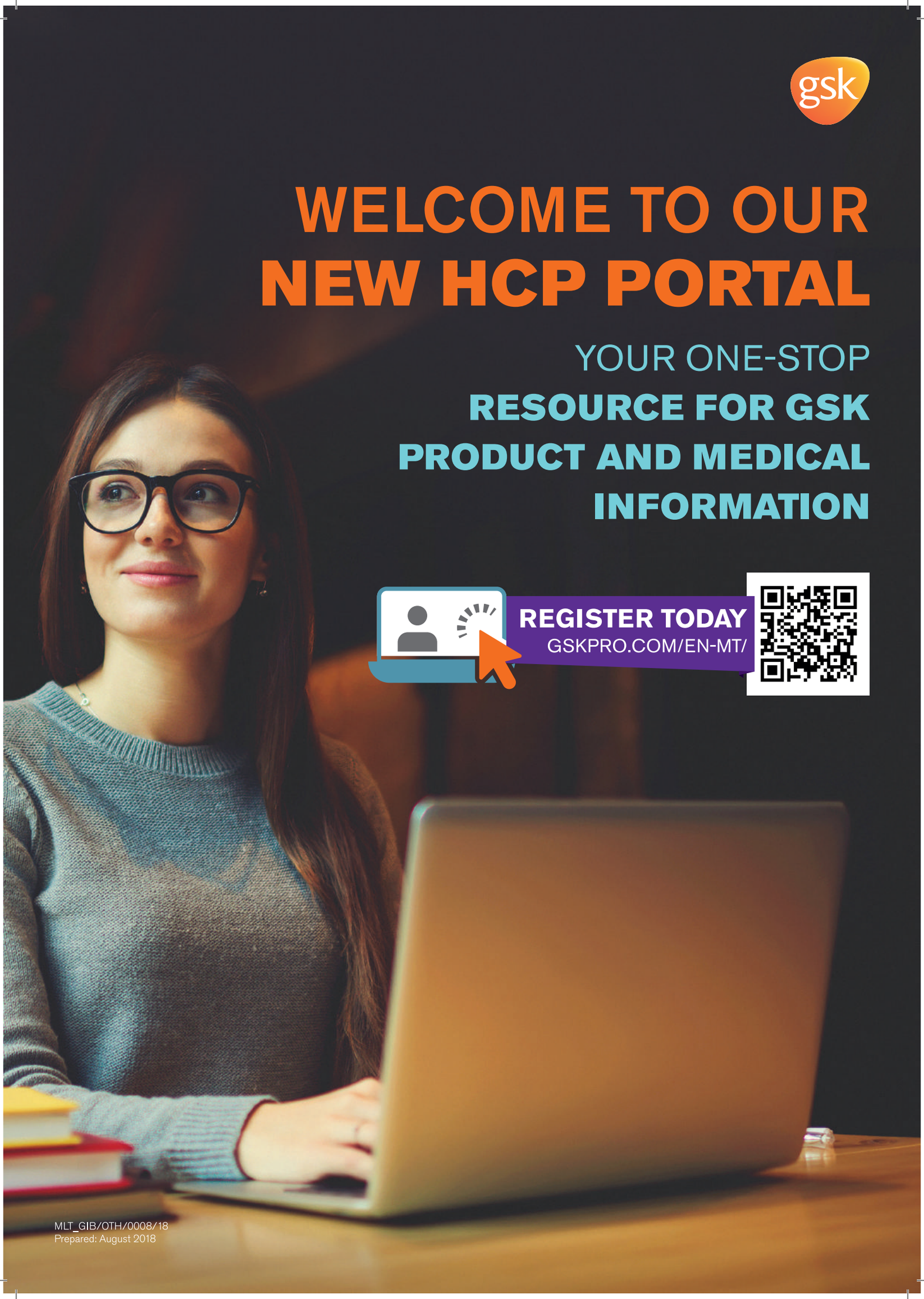
Figure 7. Two CT scans obtained one year apart in a 77-year old woman showing a right renal tumour that has increased in size from 12mm (arrow) to 14mm in diameter in the interval. Continuing with active observation is the ideal approach in these circumstances.

that laparoscopic guidance and can be done under local anaesthesia. Imaging-guided core biopsy should always be performed prior to thermal ablation. Patients undergoing thermal ablation must be informed of an increased likelihood of persistence or recurrence of the tumour, which can be addressed by repeating the ablation.

In patients who are unfit for or unwilling to accept surgery and who have a non-aggressive appearing lesion, active observation with sequential imaging is advised. Active surveillance according to AUA guidelines should be used when anticipated risks of intervention or competing risks of death outweigh the potential benefits of active treatment. The said guidelines also state that active surveillance may be used as an initial management option in patients with suspicious lesions <2cm in diameter (Fig 7). However, the patient must clearly understand the risks of tumour growth and the importance of returning for a follow-up CT scan in 3-6 months. If lesion size increases to >3cm, if there is a growth rate of >5mm per year, or if there is an increase in tumour stage, a change in treatment strategy should be offered.

In summary, the current tendency is to move away from radical nephrectomy to nephron-sparing procedures for Stage 1 and 2 renal tumours. The increasing evidence that smaller tumours may be less aggressive or even indolent has changed recommended treatment protocols to favour more conservative surgery, thermal ablation or even active monitoring with imaging.

Figure 5. CT scan showing a Stage 1 lesion consisting of a 3cm mass (arrows) in the lower pole of the left kidney that demonstrates heterogeneous enhancement with central necrosis; the tiny peripheral nodules adjacent to the renal capsule represent blood vessels and not tumour extension. The renal vein (arrowheads) is filled with contrast material confirming absence of intravascular extension of the tumour.


gsk
WELCOME TO OUR
NEW HCP PORTAL
YOUR ONE-STOP
RESOURCE FOR GSK
PRODUCT AND MEDICAL
INFORMATION
REGISTER TODAY
GSKPRO.COM/EN-MT/
MLT_GIB/OTH/0008/18
Prepared: August 2018