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DR IAN ELLUL

Suicides - The Elephant in the Room

Target 3.4 of the Sustainable Development Goals adopted by the United Nations relates to the reduction of mortality from non-communicable diseases and the promotion of mental health i.e. by 2030, reduction by one third of premature mortality from non-communicable diseases through prevention and treatment, and promotion of mental health and well-being. *Is Malta on the right track to achieve target 3.4?*

Mental health problems affect a nation's wealth, productivity and well-being both directly and indirectly. Using the traditional human capital approach, the costs of mental disorders globally have been estimated to be approx. €2 trillion in 2010. Nonetheless, using the Value of Statistical Life to calculate the economic impact of mental disorders – quantifying subjective risk-values - the global economic burden of mental disorders has been estimated at €7.2 trillion in 2010, higher than that of oncology, chronic respiratory illnesses, and diabetes. This economic burden is expected to almost double until 2030.[1] Mental disorders also constitute the 3rd leading cause of overall disease burden (as measured by disability-adjusted life-years), following cardiovascular disease and oncology, in the WHO European Region.[2]

A recent reply to PQ No. 8828 of the 14th legislature of the Maltese Parliament in May 2023 clearly states that during the last 10 years there were 261 suicides in Malta with the ages of the victims ranging <25 years to >75 years. Of note is the fact that the Maltese population has increased considerably during the past decade.

The numbers speak for themselves. If one would include all attempts of suicides, the numbers would logically be much higher. In 2023, a total of 12 suicides were registered over 5 months between January and May alone. It is worrying that during the past decade we have seen no improvement in local suicide numbers which mostly affected men and non-foreigners. Such inertia needs to be addressed with urgency. **Indeed, the collective number of suicides <25 years of age which occurred since 2021 [at least 10 suicides] have reached those reported collectively during the preceding 6 years [2015 – 2020]**, and we are still in Q3 of 2023. In keeping with this, the pernicious effects of the recent advent of social media should be considered.

The reasons which lead to the contemplation and eventually, to a suicide attempt, are multi-factorial and these may include personal, familial, economic and societal challenges which are faced by the victim. Indeed, many times the person who contemplates a suicide is a victim of circumstance. Their family is often also a victim. Let us never forget this.

The Maltese Government and the Maltese Society must actively contribute more to mitigate the challenges faced by vulnerable subpopulations in Malta. One must not only translate these suicide numbers into years of productive life lost and economic value of lost productivity. We must not risk missing the forest for the trees.

Recently, media reported for example, that on 20 July, Mount Carmel Hospital was left for 4 hours in pitch darkness without electricity at night during a heatwave since the generators failed to start up, to the detriment of healthcare professionals and vulnerable patients alike. The kernel of the matter here is not power cuts since these may happen during prolonged heat waves; rather, it is the lack of appropriate generator backup in Mount Carmel Hospital. Such incidents should never occur.

In keeping with this, the provision of mental health services should be prioritised, including facilities and staff. The much awaited *Mental Health Strategy for Malta 2020-2030* published in 2019 stated that Malta will have a new acute psychiatric hospital and that Mount Carmel Hospital, built in 1861, will be renovated. Of note is the fact that such renovation has now been scaled down.[3]

It is important that we, all of us, embark and champion a national strategy which engages community members in shared activities, supports socio-emotional learning programs, teaches parenting skills to improve family relationships and supports resilience through educational programs. Such concerted efforts, spearheaded by the Maltese Government, should include as many stakeholders as possible including our extended families, schools, football clubs, band clubs, Scouts, etc to help percolate thoroughly in our societal strata and modify the granular forma mentis of our culture which is constantly evolving. The future is ours to embrace but we must champion the rights of our precious vulnerable subpopulations.

Let us be bold and be an advocate of those who require help. The ones who need it most may be the ones who search the least for it. Help may be sought from 1770 (Richmond Foundation), Suicide Prevention, Outreach and Therapeutic (SPOT) services by appointment on 21228333 (Victim Support Malta) and 179 (FSWS). Anonymous chats such as kellimni.com are also available locally. Public officers can seek the help of the Employee Support Programme (ESP) on 22001210, by appointment.

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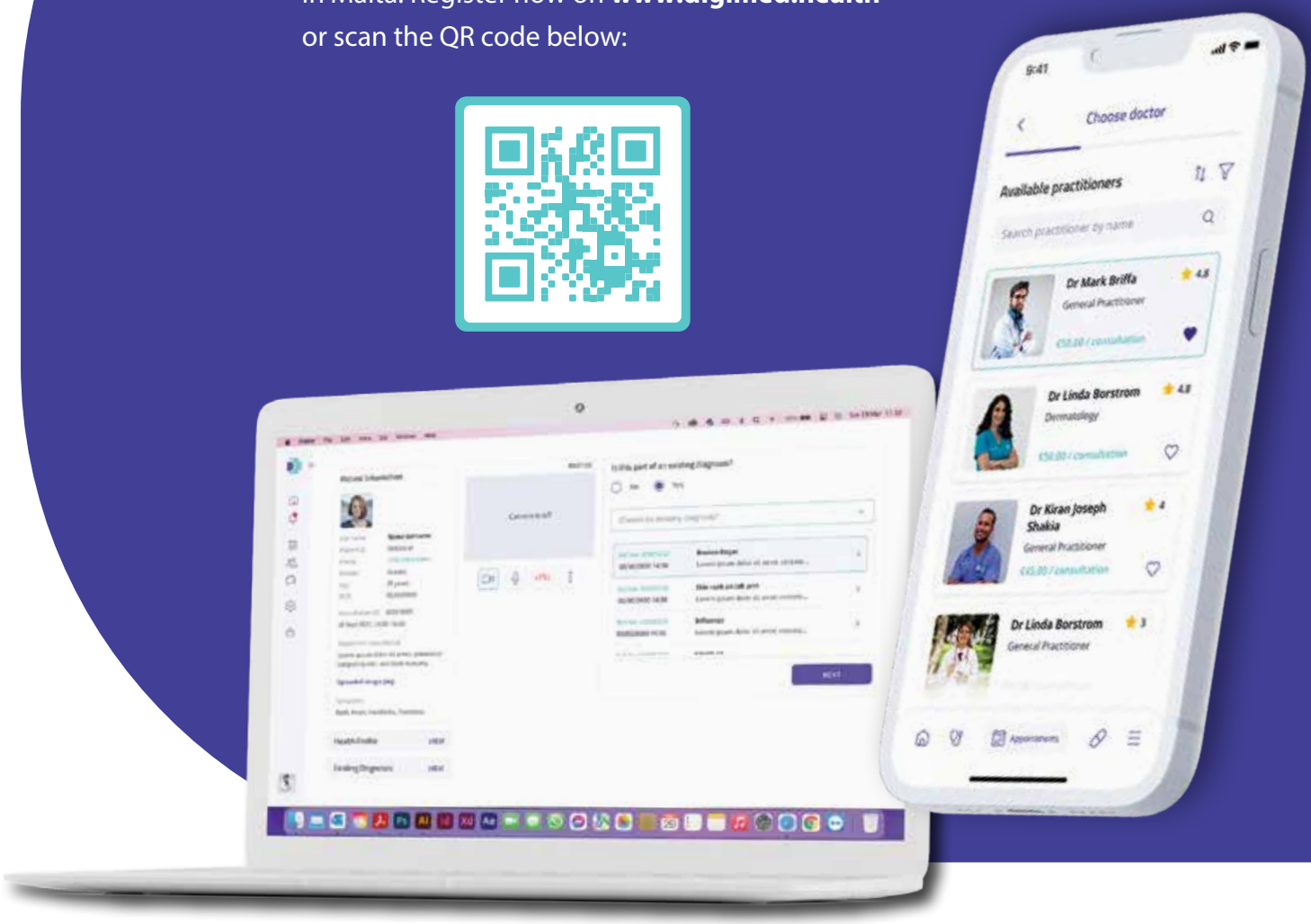

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Issue Guide

Authors

Dr Seren Cakar MD is a dedicated Foundation Year doctor with a keen interest in obstetrics and gynaecology. Her goal is to contribute to the advancement of women's healthcare through ongoing research, and commitment to continuous growth in her chosen specialty. The co-authors of the article are Dr Gabriel Tabone, Dr Sharona Falzon and Dr Mandy Collict.

Dr Gabriel Tabone MD graduated from the University of Malta in 2021. Throughout his training as a Foundation Year doctor, his distinctive interest in research and hands-on learning has led him to develop a special interest in surgery.

Dr Lara Sammut MD (Melit) MRCS (Edin) FRCR EDiR is a Radiologist at Mater Dei Hospital, St James Hospital and the National Breast Screening Unit. She specializes in Breast Imaging including image-guided breast intervention.

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Dr Alfred Grech MD graduated from the University of Malta in 1985. He has been working in Primary Health 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-authors of the article are Dr Mario Farrugia and Dr Michael Balzan.

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FABIO SPERANDEI,
President of Novartis Cyprus and Malta and Head of the Innovative Medicines Business unit.

Novartis Malta – We Are Here to Stay

DR IAN ELLUL MEETS UP WITH **FABIO SPERANDEI** PRESIDENT OF NOVARTIS CYPRUS AND MALTA AND HEAD OF THE INNOVATIVE MEDICINES BUSINESS UNIT. WE DISCUSS THE GARGANTUAN INVESTMENT BEING DONE GLOBALLY BY THE COMPANY IN THE FIELD OF HEALTHCARE, AND HOW MALTESE PATIENTS STAND TO BENEFIT FROM THE WELL-GROUNDED AND CONTINUED PRESENCE OF NOVARTIS IN MALTA, ESPECIALLY WITH RESPECT TO ACCESS TO NEW INNOVATIVE MEDICINES.

WHO IS FABIO SPERANDEI?

I can describe myself in three phrases: inquisitive nature, passionate on my endeavours and a drive to perform, but before that, I am a husband, father of three children and a person who truly cares about relationships. My last twenty years working for Novartis have nurtured my passion for meeting people and developing meaningful relations. I have lived in many countries from Malaysia and Singapore to UK, Germany and Cyprus, where I learnt how to be inquisitive and adapt to new cultures, new methods of interactions with doctors, patients, and authorities, as well as new ways of leading and of course, being led. Communication is key to acculturate in new environments. Obviously, my degree in Economics from La Sapienza University, Rome and my Masters in Marketing have helped my numerous cycles of adaptation, but I also inherently relish working in different environments, being a very curious person who likes novelty and developing new talents.

WHERE IS NOVARTIS' REPRESENTATIVE OFFICE LOCATED IN MALTA?

Novartis, which is a global healthcare company based in Switzerland, has been in Malta since the merger of Sandoz and Ciba-Geigy in 1996, and has had a representative office in Malta for over 10 years. I take pride in stating that Novartis is currently the only innovative pharmaceutical company with its own office and personnel in Malta. The local Novartis premises are located at *Ewropa Business Centre, Dun Karm Street, Birkirkara.*

IN 2022 NOVARTIS ANNOUNCED A NEW GLOBAL ORGANIZATIONAL STRUCTURE TO ACCELERATE GROWTH, STRENGTHEN THE PRODUCT PIPELINE AND INCREASE PRODUCTIVITY. THIS 'TRANSFORMATION FOR GROWTH' BROUGHT MANY CHANGES IN SEVERAL COUNTRIES, INCLUDING MALTA. CAN YOU ELABORATE?

A new simplified structure and operational set-up has been successfully implemented during the past weeks in Malta to support the Novartis strategy to herald the next phase with a focus on innovation, growth, and productivity.

Novartis has been created more than 25 years. In the past we adopted a split commercial structure; we were essentially a Primary Care business together with an Oncology business. Over time, as we evolved from a Primary Care to a specialty pharmaceuticals business focused on innovative medicines and technologies, the boundaries between our commercial organizations became increasingly intertwined and blurred. This convolution in running two commercial structures across geographies created complexity which is undesirable. At the same time, although in the past we have seen global dramatic improvements in the lives of patients, essential patient needs remain unmet. Non-communicable diseases (NCDs), including cancer and cardiovascular disease, cause 41 million global preventable deaths each year, approximately six times the number of people who have reportedly died from COVID-19 so far. Cardiovascular diseases are the major cause of death with 18 million deaths annually, representing 32% of global deaths; 10 million lives are lost annually due to cancer, while on average 10 years are lived with disease or chronic condition globally. This is why Novartis took such a logical decision to integrate Novartis Pharma and Novartis Oncology into the Innovative Medicines business which will increase focus, strengthen competitiveness, and drive synergies.

Transition to a new simplified structure obviously affects people's life. Our purpose and our strategy continue to guide us in our seminal work. In Malta we are here to stay, true to our purpose: to help Maltese people live longer and lead better lives. This is why we decided to remain in Malta, despite the country's small size.

We decided to invest in our own resources because we want our physical presence to resonate amongst Maltese healthcare providers, government entities, and patients alike.

NOVARTIS HAS RECENTLY COMMISSIONED DELOITTE MALTA TO INVESTIGATE THE IMPACT OF SPECIFIC DISEASES ON THE GDP OF MALTA SINCE TREATING A DISEASE DOES NOT SIMPLY ENTAIL PAYING FOR A TREATMENT TO CURE A SPECIFIC DISEASE OR MAINTAIN A REMISSION

The *Transformation for Growth* strategy will thus merge the corporate strategy, the R&D portfolio, and the business development to further strengthen the Novartis pipeline with transformational medicines. Through the new structure, we aim to continue building on the prestigious work carried out over the past years by our Maltese Novartis colleagues.

WHAT IS THE NEW STRUCTURE FOR MALTA?

The new structure for Malta has been completed in the last few weeks. There are both field-based associates who will nurture customer relationships, as well as a strong regulatory team based locally with a direct link to our Basel Headquarters in Switzerland. Malta and Cyprus are working strongly together with a number of roles covering both islands. For example, I am President of Novartis Cyprus and Malta and Head of the Innovative Medicines Business unit.

WHO ARE THE FIELD-BASED ASSOCIATES IN MALTA?

Doctors and pharmacists can contact directly Ms Tania Borg and Ms Kristina Schiavone. Both will continue visiting doctors and pharmacists, but Ms Borg is also responsible to effectively support the introduction of new innovative medicines into market. Market access is our biggest challenge but also, our greatest opportunity for growth.

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NOVARTIS INVESTS APPROX. 10 BILLION USD IN R&D ANNUALLY - ONE OF THE HIGHEST INVESTMENTS NOT ONLY IN THE PHARMACEUTICAL SECTOR BUT ALSO IN GLOBAL BUSINESS IN GENERAL. HOWEVER, LESS THAN 1% OF RESEARCHED DRUGS REACH THE MARKET. WE ALSO EXPERIENCE INCREASINGLY STRINGENT REGULATIONS FOR THE PHARMACEUTICAL SECTOR. HOW SHOULD THE BUSINESS MODEL IN THE SECTOR EVOLVE IN THE FUTURE?

Novartis consistently invests a significant amount of its annual total revenue as R&D. This stems from the fact that along the years Novartis has evolved into an innovative medicines company, with five dominant platforms to bring life-changing treatments to patients: chemistry & chemical biology, biotherapeutics, cell therapies, gene therapies & radioligand therapies (RLT), with an increased granular approach to biologicals and advanced technology platforms. Novartis has a deep fast-growing pipeline across its core therapeutic areas i.e. cardiovascular, immunology, neuroscience, solid tumors and hematology. We have over 150 pipeline projects and 90% of our treatments in development have the potential to be first-in-class or first in a specific indication. In keeping with the company's strategy to invest in new medicines, earlier this year Novartis acquired DTx Pharma to develop siRNA therapies for neuroscience indications, and Chinook Therapeutics with a view to expand the company's renal portfolio in rare diseases.

Over the past years, we have seen increasingly high demands on healthcare, and the spending on healthcare systems by governments is growing exponentially across all countries. I believe that governments and the pharmaceutical industry need to partner and work together towards a common goal i.e. to improve the access of innovative medicines to patients in a more equitable and timely manner.

I strongly believe that investment in the healthcare sector including R&D, digitalization of health care systems, including tools to enhance collaboration with medical professionals, as well as alliances/partnerships, including those with patient advocacy groups, is truly an investment not a cost.

WHY IS IT IMPORTANT TO INVEST IN INNOVATIVE MEDICINES?

Innovation has the power to improve patients' lives. There is no yellow-brick road to address gaps in clinical care. However, innovative medicines offer treatments with greater efficacy to possibly bridge these gaps. This can translate into improved social impact: higher level of well-being, increased productivity (for both paid and unpaid activities), and disability-free life expectancy (healthy life years), also stemming from less hospitalizations. This in turn leads to a better quality of life (QoL) and less burden on the Maltese hospital services. Everyone stands to gain.

Novartis is well-positioned in R&D with respect to advanced therapies and the integration of genomics, proteomics and other -omics technologies for the development of personalized and targeted treatments. Indeed, Novartis has been a trailblazer with the introduction of the small interfering RNA (siRNA) inclisiran and the chimeric antigen receptor (CAR) T-cell therapy tisagenlecleucel. The ultimate goal of our R&D is to develop innovative medicines with increased efficacy and minimized adverse reactions with a view to improve the disability-free life expectancy.

Novartis talks the talk and walks the walk. Novartis has recently commissioned Deloitte Malta to investigate the impact of specific diseases on the GDP of Malta since treating a disease does not simply entail paying for a treatment to cure a specific disease or maintain a remission. We believe that investing in prevention will positively impact the Maltese national budget. There are many other ramifications including potential gains in productive life of patients as well as their carers, which have important socio-economic implications.

If Malta wants to maintain a sustainable economic growth, the Maltese health authorities and policy makers need to embrace innovative medicines, similar to what other member states, big and small, are doing. Unfortunately, in Malta the sluggish pace by which innovative medicines are introduced on the Maltese Government Formulary List (including both the Hospital Formulary as well as the Outpatients Formulary), has led Malta to fall behind other countries with respect to new medications which have been marketed many years ago, to the detriment of our primary stakeholder i.e. the Maltese Patient.

IN FACT, THE EFPIA'S PATIENTS W.A.I.T. INDICATOR 2022 SURVEY PUBLISHED IN 2023 UNEQUIVOCALLY SHOWS THAT MALTESE PATIENTS HAD THE LOWEST ACCESS TO NEW INNOVATIVE MEDICINES APPROVED IN THE EU. WHAT ARE YOUR THOUGHTS ABOUT THIS?

In simple terms, Malta was ranked 35th out of 37 European countries, including the EU member states. The European Federation of Pharmaceutical Industries and Associations' Patient W.A.I.T Indicator 2022 is the largest European study looking into innovative medicines availability and the time to patient access i.e., approval on the public reimbursement formularies from 2018-2021.

The survey is based on the core concept of 'availability' which refers to the 'inclusion of a centrally approved medicine on the public reimbursement list in a country.' Based on survey data, only 10 out of 168 new innovative treatments which have been approved by EMA during this period are available to Maltese patients. The average number of available medicines among the 37 countries is 76 medicines. Germany was ranked first as 147 medicines out of 168 medicines approved by EMA are available on its market.

There is a stark difference between Malta and other EU countries, even small ones. Being President of Novartis Cyprus and Malta, I inevitably compare the two countries in terms of medicines availability. Cyprus is the 3rd smallest country in the EU in terms of population, with Malta the smallest, and it is similar to Malta in that patients with chronic conditions can access medicines free of charge from the NHS. However, I cannot fathom why the market access and penetration of Novartis in Cyprus is 3 times that of Malta, even though the population in Cyprus is not even twice that of Malta. Furthermore, the seminal question here is why medicinal products which have been on the government formulary list in Cyprus for the last 10 years are still not available on the government formulary list in Malta.

Novartis has invested and will continue investing in the country, striving to improve the availability of new medicines to Maltese patients.

SUCH GROSS DISPARITY IN ACCESS TO MEDICINES MAY BE RELATED TO THE PRICE?

This is not the case. Novartis and also other pharmaceutical companies use reference pricing to establish the price for Malta. This exercise entails using the price of a specific product in other EU member states to establish a price for that product in Malta. Novartis has a policy to propose similar pricing between member states. Considering the challenges in market access in Malta, we are trying to support the patients and provide lower prices for specific medicines since we truly believe that Maltese patients should have access to the same standard of care which is found in other countries. My conundrum is why Malta has performed very low in the W.A.I.T survey. Currently Maltese patients are paying out of pocket to have access to specific treatments. This is a sobering fact. Why are they constrained to endure such out-of-pocket expenses when other member states have these same medicinal products on the hospital formulary?

Maltese patients have the same rights of other EU patients. This is clearly reflected in the European Charter of Patients' Rights. Maltese patients have the right to be treated as early as possible with innovative treatments.

We look forward to improving access of Maltese patients to innovative medicines by collaborating and partnering with all Maltese stakeholders who have patients at heart and have the necessary goodwill to implement the necessary strategies to improve such access. We are optimistic.

NOW THAT THE NEW NOVARTIS STRUCTURE HAS BEEN FINALIZED AND THAT THE COMPANY IS MOVING AHEAD WITH A STRONG PIPELINE, WHAT IS YOUR VISION FOR NOVARTIS IN MALTA?

Novartis is committed to invest in people and its office in Malta since we want to make a difference for patients locally. As a patient-driven company we believe in forging partnerships to address the specific needs of doctors and patients alike. We need to instill and nurture a passion in all stakeholders for one common goal, to enhance equity in scientific innovation when compared with our European counterparts. Hopefully this will percolate through all societal strata with a view to strengthen patient advocacy groups, with an empowered patients' voice. I take pride in my team's contribution and I am equally proud to form part of Novartis.

We all have a moral obligation to ensure that no single patient is left behind. Novartis Malta is here to stay and we are committed to provide patients a chance for a brighter tomorrow. This is our pledge.

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. Splitting or crushing of the tablets is not recommended.

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 pregn,inc:y.

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. Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril/valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing medicinal 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 sacubitril/valsartan 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 sacubitril/valsartan. If hypotension occurs, temporary down-titration or discontinuation of sacubitril/valsartan 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 sacubitril/valsartan is not recommended. Use of sacubitril/valsartan 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. sacubitril/valsartan is not recommended in patients with end-stage renal disease. Hyperkalaemia: Treatment 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. If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with sacubitril/valsartan. If angioedema occurs, discontinue sacubitril/valsartan immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. It 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 Tu.: 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 sacubitril/valsartan because it is a neprilysin substrate. Psychiatric disorders: Psychiatric events such as hallucinations, paranoia and sleep disorders, in context of psychotic events, have been associated with sacubitril/valsartan use. If a patient experiences such events, discontinuation of sacubitril/valsartan tre,itment should be considered

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 sacubitril/valsartan with statins or PDE5 inhibitors. No clinically relevant interaction was observed when simvastatin and sacubitril/valsartan were co-administered. Monitoring serum potassium is recommended if sacubitril/valsartan 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 sacubitril/valsartan who are taking NSAIDs concomitantly Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists including sacubitril/valsartan. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of sacubitril/valsartan and furosemide reduced C_m and AUC of furosemide by 50% and 28%, respectively, with ;:educed urinary excretion of sodium. Co-administration of nitroglycerin and sacubitril/ valsartan 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 sacubitril/valsartan 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 sacubitril/valsartan with metformin reduced both C_{max} and AUC of metformin by 23%. When initiating therapy with sacubitril/valsartan in patients receiving metformin, the clinical status of the patient should be evaluated.

Fertility, pregnancy and lactation: The use of sacubitril/valsartan 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 sacubitril/valsartan 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 sacubitril/valsartan 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.

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DR DANIEL CILIA, DR MARTHA DARMANIN, PROFESSOR ROBERT SCIBERRAS

Audit on Oxygen Prescription in Adult Inpatient Wards at the Gozo General Hospital

ABSTRACT

Oxygen is crucial in the delivery of inpatient care. An audit regarding oxygen prescription and administration in adult inpatient wards at the Gozo General Hospital was carried out between December 2022 and January 2023. Data was collected by reviewing emergency department and inpatient ward treatment charts and admission plans. Results acquired were then compared to a similar audit done in Malta. Both audits concluded that oxygen documentation and prescription tend to be overlooked. Hence, we recommend that further education and awareness is given to this domain of patient care to improve outcomes and reduce likelihood of adverse events.

Keywords: Oxygen, Documentation, Prescription, Patient safety

INTRODUCTION

Oxygen is crucial in the treatment of patients with acute illness. However, despite its frequent use in both emergency and inpatient settings, appropriate prescription, documentation on treatment charts, and regular review of oxygen therapy tend to be neglected. The British Thoracic Society Guidelines[1] recommend specifying target oxygen saturations and appropriate delivery methods for each patient in their treatment chart to ensure safety. Inappropriate oxygen delivery or hypoxia in the context of type 2 respiratory failure can be fatal and potentially harmful to the patient; this highlights the importance of accurate prescription and administration of oxygen therapy.

METHODOLOGY AND AIMS

Data was retrospectively gathered from patient hospitalizations at the Gozo General Hospital's (GGH) emergency department (ED) and adult inpatient wards (Male General Ward, Female General Ward, Critical Care Unit and Day Care Unit) over the course of six weeks between December 2022 and January 2023, after acquiring approval from the lead consultant at GGH and the data protection officer. Data was gathered by reviewing the patient's emergency admission sheet and treatment chart, followed by an analysis of the inpatient treatment chart and the admission plan in the ward.

A self-constructed data collection sheet was created to maintain full patient confidentiality with no possibility of patient identification. Data collected was then analysed, with the intention of determining whether oxygen prescriptions were documented on treatment charts. Any patient in a hospital setting has the possibility of acutely deteriorating leading to development of hypoxemia. In view of this, target saturation ranges, means of oxygen delivery devices and flow rate must be specified in the patient's treatment chart, to avoid detrimental outcomes while simultaneously allowing clinicians to safely titre oxygen delivery. Patients were not contacted at any stage of the data collection, analysis, and study reporting.

The data collected included the following information:

- Admission date
- Oxygen saturation at ED
- Use of oxygen at ED
- Oxygen prescription on ED treatment chart
- Oxygen on ED plan
- Oxygen on ward plan
- Oxygen prescription on Ward Treatment chart
- Method of oxygen delivery on ward.

This audit's primary objective is to check whether prescription and documentation for oxygen therapy, for patients transferred from ED to the inpatient ward, is done appropriately. Accurate and detailed documentation of prescribed oxygen therapy plays a crucial role in reducing the risk of errors or complications that may harm the patient. It also facilitates effective communication among health care professionals during handovers or shift changes. By reviewing the documented information, incoming staff can swiftly grasp the patient's oxygen requirements and any specific considerations, promoting continuity of care and minimizing the chances of errors or miscommunication.

RESULTS

A total cohort of 229 patients were recruited over the 6-week data collection period. From these individuals, 59 patients required oxygen therapy in either the ED or the ward, for the medical diagnosis specified in Table 1.

Inclusion criteria:

Patients admitted to the general medical wards and coronary care unit with:

- Asthma exacerbation
- COPD exacerbation
- Exacerbation of Congestive Heart Failure
- Pneumonia / Bronchitis (including COVID-19)
- Pulmonary Embolism
- Inhalation of fumes
- Syncope
- Sepsis
- Diabetic ketoacidosis
- Overdose with illicit substances
- Pneumothorax
- Acute Coronary Syndrome
- Uncertain diagnosis (atypical chest pain or Shortness of Breath) requiring oxygen therapy.

Exclusion criteria:

- Patients less than 16 years of age
- Patients requiring immediate transfer to Mater Dei Hospital after presenting to Emergency at GGH
- Patients who voluntarily discharged against medical advice on initial presentation
- Re-admissions over the data collection period.

...DATA FROM THIS AUDIT SHOWS THAT 66% OF PATIENTS WHO NEEDED OXYGEN TREATMENT DID NOT HAVE ANY RECORD OF THIS WHEN THEY WERE TRANSFERRED FROM EMERGENCY CARE

Table 1. Rationale for the use of oxygen.

Diagnosis	Number of Patients Admitted
Bradycardia	1
Asthma exacerbation	1
COPD Exacerbation	7
CHF Exacerbation	13
Pneumonia (including COVID-19)	21
PE	1
Inhalation of fumes	4
Syncope	1
Sepsis	1
DKA	1
OD	1
Chest Pain	2
Pneumothorax	1
Uncertain diagnosis	4
Total	**59**

From the 59 patients receiving oxygen at GGH, in either the ED or the ward, 39 individuals did not have a specific prescription for this documented in their treatment charts. This was noted in both the ED and the Inpatient Wards.

Table 2 presents the types of oxygen delivery devices adopted for the various patients.

Table 2. Types of oxygen delivery devices adopted for the patients.

Mode of Delivery	Number of Patients	Percentage
Nasal Cannulae	11	18.6%
Normal Face Mask	28	47.4%
Tracheostomy Mask	2	3.4%
Venturi Mask	8	13.6%
Non-Rebreather Mask	7	11.9%
Non-Invasive Ventilation	2	3.4%
Intubation	1	1.7%
Total	**59**	**100%**

In the ED, oxygen was administered to 51 patients. Out of these only 14 patients had the treatment specifically mentioned in the ED treatment chart. This represents only 28% of the total number of patients that were actually administered oxygen in the ED (Figure 1).

Figure 1. Patients on Oxygen in the Emergency Department.

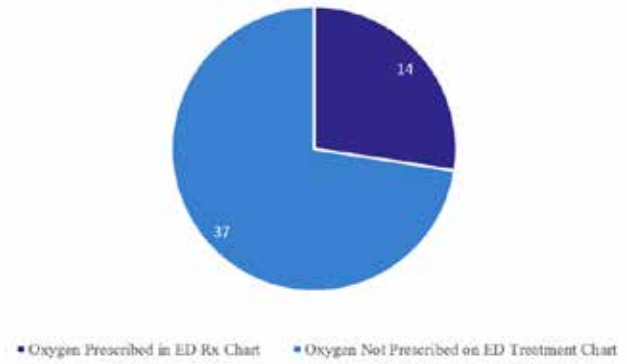
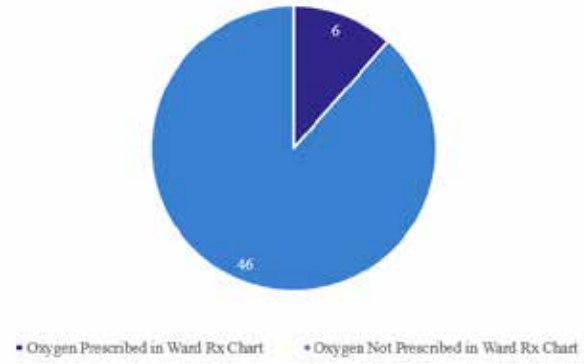


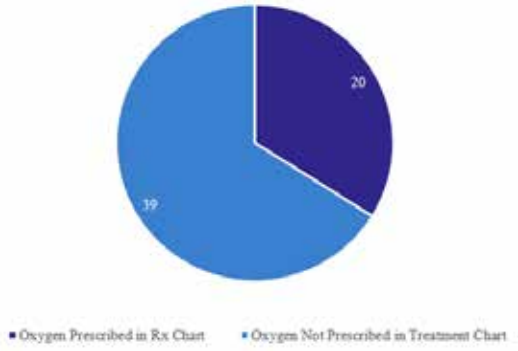
Figure 2 shows that out of 52 patients receiving oxygen in the ward, only six had oxygen prescribed in their treatment charts. This represents only 13% of the patients that were actually receiving oxygen treatment in the ward.

Figure 2. Patients on Oxygen in the Ward.



When the ED and ward treatment charts were compared, it was noted that out of the total number of patients receiving oxygen treatment in either the ED or the ward (59 patients), only 20 patients had oxygen prescribed in either their ED or ward treatment chart. This represents 34% of the total number of patients receiving oxygen treatment.

Figure 3. Total Patients on Oxygen in the Emergency Department and Wards.



In conclusion, Figure 4 presents the data summary of the prescribed oxygen therapy in the treatment charts versus that actually administered oxygen therapy in both the ED and the wards, separately. Furthermore, the overall combined data of ED and wards is also presented, reflecting the GGH scenario, following a comparative analysis of all treatment charts.

Figure 4. ED and Wards data summary reflecting prescribed oxygen therapy in treatment charts and actually administered oxygen therapy; Including combined data of audited departments.

Total Number of Patients: 229

Number of Patients on Oxygen in ED/Ward: 59

Oxygen prescribed in ED/Ward Rx Chart: 20

EMERGENCY DEPARTMENT	WARDS
Number of Patients on Oxygen: 51	Number of Patients on Oxygen: 52
Oxygen prescribed in ED Rx Chart: 14	Oxygen prescribed in Wards' Rx Chart: 6

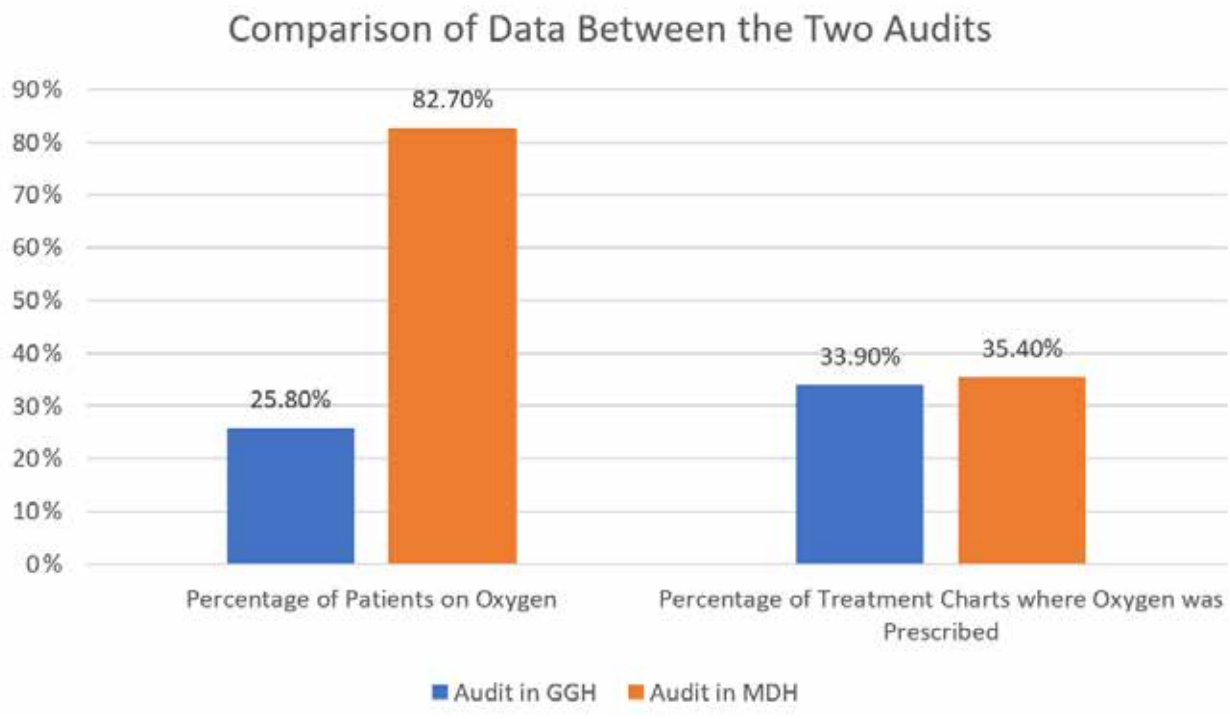
The results of this audit were compared to a similar, albeit more extensive, audit performed by Borg Azzopardi et al.[2] in 2022 at Mater Dei Hospital, the only other public general hospital in the Maltese islands. This audit consisted of 300 patients, of whom 248 (83%) were on oxygen. When compared to the percentage of patients on oxygen in the current audit, which was 26%, there is an evident discrepancy (Figure 5). However, it is important to note that this can be explained by the smaller pool of patients in GGH and the fact that in the audit done in MDH, only patients who presented with shortness of breath were considered (i.e. there was a higher chance of them being on oxygen). Despite this difference in numbers, the proportion of patients to whom oxygen was prescribed on the treatment chart when indicated, is comparable. In fact, the audit done in MDH, showed that 35% of the patients on oxygen had it prescribed in their treatment charts, while, similarly, in the current audit the percentage was of 34%. Therefore, in both MDH and GGH, the oxygen prescribed in management plans was written in the patient's treatment chart in little more than 1/3 of patients. This means that approximately 2/3 of patients required oxygen and this was not prescribed in their treatment chart. This could lead to serious consequences as discussed below. The following bar chart shows how the two audits compare to each other.

DISCUSSION

A significant proportion of patients admitted during the previously stipulated timeframe were accounted for by cases of both bacterial and COVID-19 pneumonias, CHF exacerbations and COPD exacerbations. In fact, these presentations accounted for 69% of the total cohort group which required some form of supplemental oxygen therapy at emergency or an inpatient level. According to the BTS guidelines, supplemental oxygen is warranted in instances were oxygen saturations fall below 94% or else are less than 88% in chronic obstructive airway disease patients. Moreover, the guidelines also highlight the importance of specifying the targeted oxygen range, suitable oxygen delivery device and flow rates for all patients transferred to an inpatient setting, as a safety netting in the case of acute deterioration in clinical state.[3]

If a patient's oxygen needs are not met, oxygen therapy, like all other forms of treatment, can have serious side effects. The development of oxygen imbalances like hypoxemia can lead to adverse effects such as lactic acidosis, myocardial ischaemia secondary to coronary vasodilation and pulmonary hypertension. In contrast, hyperoxia may give rise to cerebrovascular accidents, decreased renal blood flow with ensuing acute tubular necrosis, atelectasis, and decreased ventilation in patients with hypercapnic respiratory failure. This makes it the more important to stress the importance of carefully contemplating oxygen therapy given the circumstances at hand, as well as the implications of its documentation

Figure 5. Data Comparison between MDH 2022 Audit[2] and GGH Audit.



and prescription.[4] Despite this, data from this audit shows that 66% of patients who needed oxygen treatment did not have any record of this when they were transferred from emergency care. They also did not have information about the desired saturation ranges or the preferred manner of delivery.

The data collected suggests that inattention to the prescription of oxygen on treatment charts is a significant issue in both emergency and ward settings. Specifically, the figures indicate that a substantial proportion of patients in these settings did not have any form of oxygen prescription - with 73% of patients at emergency and 89% of those in an inpatient setting not receiving appropriate oxygen prescription. This alarming trend highlights the potential risks and consequences that patients face due to suboptimal oxygen therapy practices. The absence of proper oxygen prescription can lead to inadequate monitoring of oxygen saturation levels, resulting in inefficiencies and substandard handover of patient care. This could be particularly problematic in situations where patients require continuous oxygenation, as it may lead to oxygen desaturation and harm to the patient's overall health. Thus, it is crucial to ensure that healthcare professionals prioritize accurate and adequate oxygen prescription practices to ensure the safety and well-being of patients.

Poor oxygen prescription practices in hospital treatment charts can arise due to several reasons. Medical and nursing staff may not be familiar with the oxygen prescription section on treatment charts, leading to inadequate or inappropriate prescriptions. Inadequate monitoring of patients who require oxygen therapy can hinder the determination of suitable flow rates and concentrations. Poor communication between medical staff during handover can lead to errors in prescribing and monitoring oxygen therapy. Healthcare professionals may find it challenging to alter ingrained habits, leading to suboptimal oxygen prescription practices. Additionally, healthcare professionals may over-rely on pulse oximetry and overlook other factors such as respiratory rate or level of consciousness. Prescriber biases towards higher oxygen flow rates or concentrations without considering the potential harm of hyperoxia may also contribute to poor oxygen prescription practices. Lack of awareness of the adverse events resulting from hypoxia/hyperoxia, time constraints, and limited resources may further exacerbate the problem.[5]

Adequate documentation of oxygen therapy in treatment charts can be promoted by educating healthcare personnel regarding the importance of accurate and complete documentation. This should include emphasis on the correct use of oxygen prescription charts, the importance of documenting all relevant information, and the consequences of incomplete or inaccurate documentation. The implementation of an electronic documentation systems can also improve the accuracy and completeness of oxygen therapy records by providing reminders for healthcare professionals to document all necessary information. Such a system will also enable for and facilitate easy retrieval of records which will allow for efficient and effective care of patients.[5]

LIMITATIONS

Sample size is a limitation since Gozo General Hospital caters for a small community. Another limitation is that patients who were admitted at the ED on Sundays or public holidays and needed brief oxygen therapy, but were discharged from the ED, have not been included in the study.

FUTURE RESEARCH

The audit did not investigate whether oxygen is prescribed or administered correctly. Further research in this area will indicate whether oxygen therapy is effectively being given to patients, according to established guidelines, in both the ED and in-patient wards.

CONCLUSION

The use of oxygen prescription charts is crucial in ensuring that oxygen therapy is prescribed appropriately and administered correctly. They help ensure that patients receive appropriate and safe treatment, provide a means of communication between healthcare providers, and serve as a legal record of care. Our audit results show that the majority of patients who required oxygen therapy, did not have this documented in their treatment chart.

Therefore, we recommend that staff should be educated and trained on the use of oxygen prescription charts, and regular audits should be conducted to monitor adherence to prescribed oxygen therapy. This will ensure that patients receive the appropriate oxygen therapy, which can improve their outcomes and reduce the risk of harm associated with inappropriate use of oxygen.

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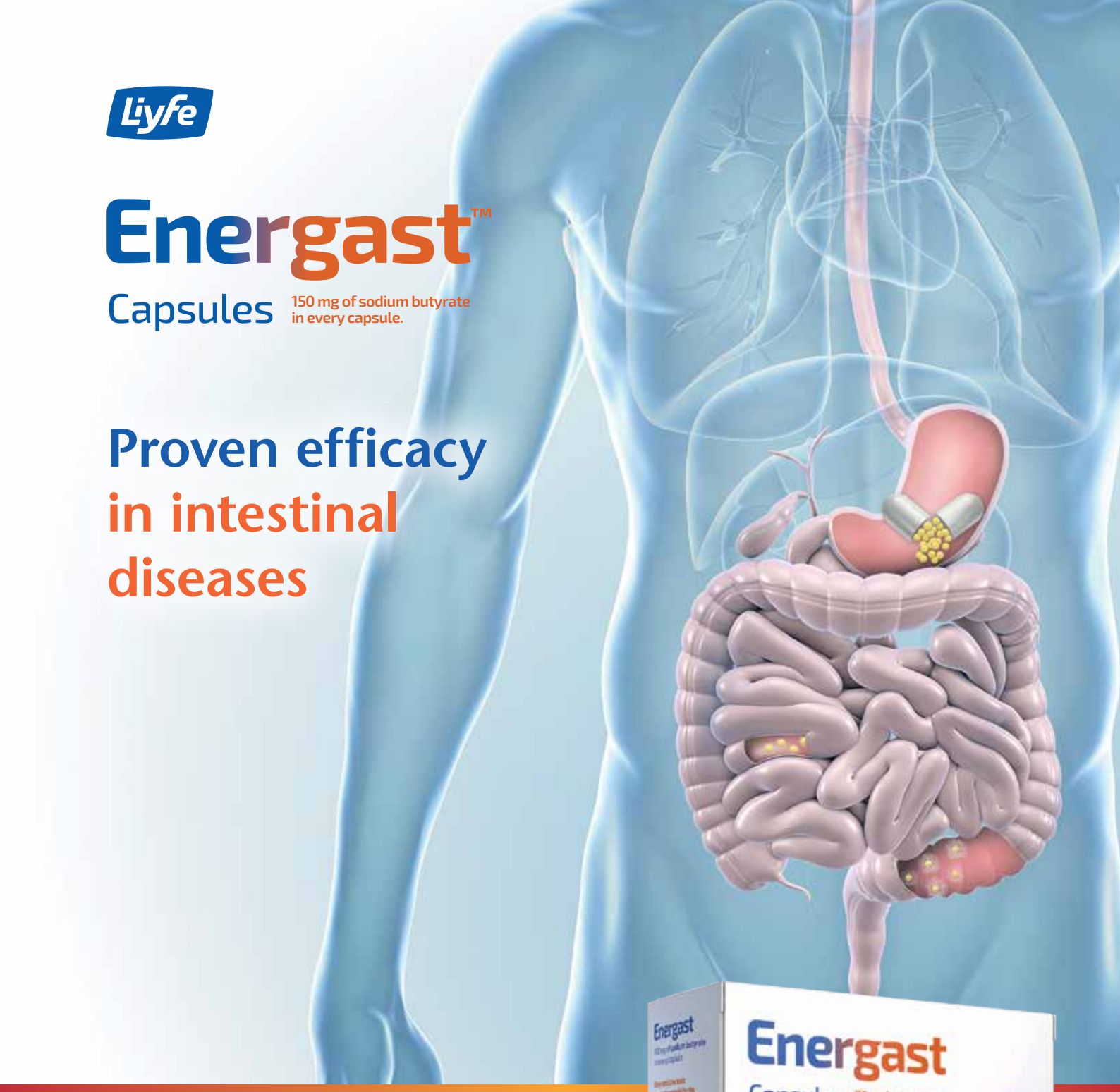

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DOSAGE: The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months. ♦*Missed doses*: If a planned dose is missed by less than 3 months, inclisiran should be administered and dosing continued according to the patient's original schedule. If a planned dose is missed by more than 3 months, a new dosing schedule should be started – inclisiran should be administered initially, again at 3 months, followed by every 6 months. ♦ *Treatment transition from monoclonal antibody PCSK9 inhibitors*: Inclisiran can be administered immediately after the last dose of a monoclonal antibody PCSK9 inhibitor. To maintain LDL-C lowering it is recommended that inclisiran is administered within 2 weeks after the last dose of a monoclonal antibody PCSK9 inhibitor. ♦*Elderly, hepatic impairment, renal impairment*: no dose adjustment is necessary. Inclisiran should be used with caution in patients with hepatic and renal impairment. ♦*Paediatric population*: The safety and efficacy of inclisiran in children aged less than 18 years have not yet been established. ♦*Method of administration*: Inclisiran is intended for administration by a healthcare professional via subcutaneous route. Each pre-filled syringe is for single use only.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

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INTERACTIONS: Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters. Therefore, inclisiran is not expected to have clinically significant interactions with other medicinal products. Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

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DR SEREN CAKAR, DR GABRIEL TABONE,
DR SHARONA FALZON, DR MANDY COLLICT

Understanding Second Trimester Miscarriages: A Comprehensive Review

ABSTRACT

Spontaneous miscarriage is the most common complication of pregnancy. Pregnancy loss is usually multifactorial and dependent on a wide variety of genetic and epigenetic risk factors affecting either the parents or the foetus including parental age, health status, lifestyle, chromosomal abnormalities and anatomical/physiological conditions. Foetal loss during the second trimester can present with a broad range of symptoms and can be more complicated than first trimester losses due to the increased risk of haemorrhage or infection. Management of second trimester miscarriage can be divided into expectant, medical, and/or surgical interventions alongside psychological support.

Key Words: Second trimester miscarriage, Chromosomal abnormalities, Thrombophilia, Foetal loss, Uterine malformations.

INTRODUCTION

Spontaneous miscarriage is the commonest pregnancy complication, occurring in about one-fifth of clinical pregnancies. A miscarriage is defined as a spontaneous foetal loss from the time of conception until 24 weeks of gestation. The majority of miscarriages occur during the first 12 weeks of pregnancy and therefore experiencing a miscarriage during the second trimester of pregnancy is quite rare and usually takes expectant parents by surprise. A miscarriage in the second trimester is defined as a pregnancy loss after the 12th week and before the 24th week of gestation.

PRESENTATION

The most common symptoms associated with sudden pregnancy loss include uncomplicated bleeding, pain, cramping or labour. While uncomplicated bleeding is the most common presentation of miscarriage, it is important to note that not all those who experience bleeding during gestation will experience pregnancy loss. After the first trimester, a miscarriage may present with more complications including haemorrhage and infection leading to haemodynamic instability. Other symptoms of pregnancy loss may be more subclinical and subjective to each respective patient such as nausea, vomiting and decreased breast tenderness amongst others.

RISK FACTORS

A second trimester miscarriage is a clinical challenge as there are multiple potential risk factors contributing to such an event.

Epidemiological Factors

Maternal age and the number of previous miscarriages are two important independent risk factors which increase the chances of a further miscarriage event. An older maternal age has a negative impact on the amount and quality of viable oocytes. Studies have also shown that advanced paternal age also contributes to a higher miscarriage risk. The highest risk was seen among couples where the female was ≥35 years old and the male ≥40 years old.[1] Moreover, the risk of miscarriage increases with the number of previous pregnancy losses, whereby a female with a history of three consecutive miscarriages has a 40% chance of foetal loss in her next pregnancy.[2]

Other environmental risk factors which are known to negatively impact a pregnancy and therefore increase the chances of a miscarriage at any gestational age include cigarette smoking, alcohol consumption and obesity.

Genetic Factors

Parental and embryological chromosomal abnormalities can also contribute to second trimester pregnancy losses. The risk of miscarriage from chromosomal abnormalities of the embryo also increases with advanced parental age. Around 24% of second trimester pregnancy losses are due to chromosomal anomalies,

most commonly trisomy 13, 16 (almost always fatal in utero), 18, 21 and monosomy X (Turner's syndrome).

Anatomical Factors

Females with uterine malformations have been noted to have higher rates of second trimester miscarriages. Studies have shown that women born with a septate uterus are more likely to miscarry in the first trimester while those with an arcuate uterus are more prone to experience a second trimester miscarriage. In fact, retrospective research concerning reproductive outcomes has demonstrated that females with untreated uterine abnormalities have a higher risk of preterm delivery and miscarriage, whereby only half experience a full-term delivery.[3] Studies have shown that surgical correction of uterine anomalies such as hysteroscopic removal of an intra-uterine septum was associated with a reduced probability of spontaneous abortion.[3,4]

Cervical incompetence is another important cause of second trimester miscarriage. The diagnosis of cervical insufficiency is usually based on a history of pregnancy loss preceded by painless cervical dilatation and spontaneous rupture of membranes. Factors which may contribute to a higher incidence of cervical incompetence include previous cervical trauma such as cone biopsy, high parity, and prior foetal losses during the second trimester.

Infective Agents

Infection has been shown to account to 10-25% of second trimester miscarriages, especially in developing countries due to a multitude of factors including higher rates of vector-borne infections such as syphilis and malaria as well as region-dependant barriers to appropriate healthcare.[5,6] The presence of bacterial vaginosis during the first three months of pregnancy is an independent risk factor for second trimester miscarriage and preterm delivery. A randomised controlled trial has outlined the importance of treating bacterial vaginosis early on with clindamycin in order to reduce the incidence of a second trimester miscarriage or preterm labour.[7]

Thrombophilia

A retrospective meta-analysis on the impact of inherited and acquired thrombophilia disorders in miscarriages showed that a non-recurrent pregnancy loss between 20 to 24 weeks gestation is strongly associated with factor V Leiden, protein S deficiency and the prothrombin gene mutation.[8] Thrombophilias have been considered as a cause for recurrent miscarriages and late pregnancy complications, namely due to thrombosis of the uteroplacental circulation.

The presence of anti-apolipoprotein H antibodies, specifically anticardiolipin and lupus anticoagulant in females with systemic lupus erythematosus, antiphospholipid syndrome or other immunologic disorders are a principal risk factor contributing to second and third trimester miscarriages. Such antibodies give rise to placental thrombosis and thus all females with a history of one or more second trimester foetal loss should be screened for possible hypercoagulable state disorders.

MANAGEMENT

The management of second trimester miscarriages depends on the clinical presentation of the woman and the underlying cause of the pregnancy loss. In cases where the miscarriage is inevitable, expectant, medical or surgical management can be offered to the patient.

Expectant management is reserved for clinically stable patients in whom the miscarriage is allowed to occur naturally without any medical intervention.

Medical management involves the use of medications such as misoprostol to induce uterine contractions and expel the products of conception. This method is usually preferred in cases where the woman is stable and has no signs of infection. The success rate of medical management varies however, it is generally very high and can be associated with minimal discomfort and side-effects.

Evacuation of the retained products of conception (ERPC) is a procedure usually performed under general anaesthesia for the surgical management of a miscarriage after diagnosis is confirmed. The success rate of surgical management is also high, however, it carries a higher risk of complications such as bleeding, infection and uterine perforation.

Psychological Support

The loss of a pregnancy can be a traumatic experience for the couple. It is important that healthcare professionals provide adequate psychological support to all parties involved during this difficult time. Counselling and support groups can help such patients cope with the emotional distress associated with the loss of a pregnancy.[9]

PREVENTION OF SECOND TRIMESTER MISCARRIAGES

While some risk factors for second trimester miscarriages are not reversible, there are some risk reducing interventions to prevent second trimester miscarriages. These include:

1. Maintaining a healthy lifestyle: Eating a healthy diet, engaging in regular physical activity, avoiding

cigarette smoking and excessive alcohol consumption can help reduce the risk of pregnancy loss.
2. Monitoring chronic medical conditions: Women with chronic medical conditions such as diabetes, thyroid disorders, and PCOS should work closely with their healthcare provider to manage their condition during pregnancy.
3. Genetic counselling: Couples with a history of chromosomal abnormalities should consider genetic counselling to assess their risk of future pregnancy losses and discuss options such as pre-implantation genetic testing.
4. Early detection and treatment of uterine anomalies: Women with a history of second trimester miscarriages should undergo a thorough evaluation to assess for uterine anomalies. If an anomaly is detected, early surgical intervention may be recommended in certain cases.
5. Follow up screening: Women with a history of second trimester miscarriage should be screened before the next pregnancy for antiphospholipid antibodies and thrombophilias.

CONCLUSION

A miscarriage is the most devastating outcome of a pregnancy, and while the majority of cases occur in the first trimester, the intent of this article is to highlight the importance of second trimester miscarriages as an important prognostic factor for the outcome of future pregnancies. A variety of risk factors, both genetic and epigenetic, can result in spontaneous foetal loss, most of which are difficult to pre-emptively diagnose or test for prior to conception. Other risk factors are more modifiable such as the testing for congenital uterine malformations, screening for transmissible diseases and taking into account maternal age when attempting to conceive.

Independent to the pathophysiological process of miscarriage, treatment remains largely congruent and divided into medical (hormone-assisted delivery of the foetus), surgical (removal of retained products of conception) or simply via supportive expectant management. The management and investigation into the cause of abruption of pregnancy requires a multidisciplinary approach taking primarily into careful consideration the physical and mental wellbeing of the patient.

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MARK CALLEJA, CHERYL PAPPS COMPAGNO

The Benefits of Psychological & Emotional Support for Families: THE ROLE OF THE KARL VELLA FOUNDATION

The journey of illness, especially when it culminates in the loss of a loved one, is a profoundly distressing experience. For relatives, the emotional toll can be overwhelming, leading to a cascade of psychological effects that can persist long after the acute phase of the illness or loss. Recognising this, the Karl Vella Foundation (KVF) has been at the forefront of providing holistic support to families navigating these challenging waters.

The medical community is well aware of the psychological ramifications of serious illness and death on patients. However, the ripple effects on families are profound and often overlooked. Family members may experience a vast range of emotions, varying from anticipatory grief and anxiety to post-traumatic stress and persisting bereavement disorders.[1] The emotional burden can also lead to somatic symptoms such as sleep disturbances and gastrointestinal complaints, as well as immune system suppression, and even chronic conditions like cardiovascular diseases.[2] Performing less adequately at school or work, confusion and social withdrawal are also a few of the many reactions to grief.

KVF's approach is tailored to address the unique needs of each family, ensuring that the psychological well-being of families is prioritised. Young minds are especially vulnerable to the trauma of witnessing a loved one's illness or death. The effect of grief on children and family members, and consequently their needs, depends on a number of variables which are taken into consideration such as the nature of death, the previous pattern of family security and affection, previous losses, coping style and support system.[3]

KVF's interventions for this cohort are designed to provide a safe space for expression, helping children and family members process their thoughts and emotions and equipping them with coping mechanisms. This is done in group therapy, family therapy, and/or individual therapy sessions.

On the other hand, when assisting adults who are receiving treatment overseas and their care givers, the foundation offers support that acknowledges the multifaceted challenges they face. From dealing with their emotional wellbeing to managing the demanding logistical aspects of their treatment, KVF's support is comprehensive. Emotional and psychological support commences in Malta, continues abroad through teletherapy, and pursues once again in Malta to help families re-adjust to their new experience.

Research indicates that early intervention and support can equip relatives with tools to navigate their grief, ensuring that they can face future challenges with resilience.[4] Furthermore, supportive interventions can strengthen familial bonds by addressing the psychological needs of each family member, ensuring that families can support each other effectively.[5] Early intervention and support can prevent the onset of prolonged grief disorders and post-traumatic stress, ensuring the long-term well-being of relatives.[6]

The importance of psychological support in times of distress is recognised by the medical community. By addressing the often-overlooked emotional needs of relatives, KVF aims to enhance their quality of life by strengthening their mental health. Medical professionals play a pivotal role in healing not just the physical ailments but also the emotional and psychological challenges faced by patients and their families. By referring families to established organisations like the KVF, they can ensure that their patients receive the care and support they so desperately need.

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Human Oncogenic Viruses

ABSTRACT

Human Oncogenic Viruses (HOVs) cause 17% of all cancer in humans. Most of these viruses cause common infections and their associated malignancy is only a rare end result. Their oncogenic mechanisms are diverse and complex, but research into these mechanisms is identifying new insights which have the potential to be translated into new strategies to treat viruses and their cancer.

INTRODUCTION

It was in 1842 that the Italian surgeon from Asiago, Domenico Rigoni-Stern[1] suggested that a 'transmissible agent' might be responsible for some types of human cancer. Of course, at that time there was no knowledge of viruses, but from epidemiological analysis of death certificates he observed that nuns had less cervical cancer when compared to married females and prostitutes. He also proposed that cervical cancer was connected to sexual contact.

Currently, there are seven well established Human Oncogenic Viruses (HOVs). Table 1 lists them with their year of discovery and their associated human malignancy.

Table 1. List of the seven HOVs.

Virus	Discovery	Virus Classification	Malignancy
Epstein–Barr virus (EBV)	1964	Herpesviridae dsDNA	Burkitt's lymphoma Diffuse large B-cell lymphoma Hodgkin lymphoma Undifferentiated nasopharyngeal carcinoma Gastric adenocarcinoma Leiomyosarcoma Post-transplant lymphoproliferative disease
Hepatitis B virus (HBV)	1965	Hepadnaviridae dsDNA-RT	Hepatocellular carcinoma
Human T-lymphotropic virus-1 (HTLV-1)	1980	Retroviridae ssRNA-RT, positive strand	Adult T-cell leukaemia (ATL)
Human genital papillomavirus (HPV)	1983	Papillomaviridae dsDNA	Cervical carcinoma Squamous cell head and neck carcinoma Squamous cell anal cancer Vulvar cancer
Hepatitis C virus (HCV)	1989	Flaviviridae ssRNA-RT, positive strand	Hepatocellular carcinoma Marginal zone lymphoma Diffuse large B-cell lymphoma Follicular lymphoma
Kaposi sarcoma herpesvirus (KSHV/HHV8)	1994	Herpesviridae dsDNA	Kaposi's sarcoma Primary effusion lymphoma Multicentric Castleman disease
Merkel cell polyomavirus (MCV)	2008	Polyomaviridae dsDNA	Merkel cell carcinoma

The malignancies that are associated with HOVs reflect the viruses' ability to target specific cells which they infect, the so-called 'viral cell tropism'. Specifically, HBV and HTLV-I are very restricted as they cause only one cancer, HBV causing primary hepatocellular carcinoma while HTLV-I causing adult T-cell leukaemia. HPV is restricted to squamous epithelial cancers but these occur in various body locations like the cervix, head, neck and anus. In contrast, EBV and KSHV infect a variety of tissues. EBV shows the highest 'viral cell tropisms' and is linked to various cancer types (nasopharyngeal carcinoma, gastric adenocarcinoma, lymphomas, and leiomyosarcoma). KSHV infect endothelial and post-germinal B cells causing respectively, Kaposi's sarcoma and primary effusion lymphoma and a B-cell lympho-proliferative syndrome.

As can be seen from Table 1, HOVs belong to different families of viruses. And yet they share common features enabling them to cause cancer by seizing pivotal cellular pathways of cell growth and metabolism. The molecular mechanisms involved are complex and this essay briefly highlights the main ones.

MECHANISMS OF VIRAL PERSISTENCE AND ONCOGENESIS

HOVs can perturb a plethora of cellular pathways that can lead to viral persistence and, at a later stage carcinogenesis. The following are some of them.

Attenuation of Host Immunity

When a virus infects the cells of the host, it exploits their molecular machinery to propagate itself. But the host is not passive and tries to keep its cellular integrity. Both have evolved mechanisms to settle this conflict of interest. These mechanisms involve pathways that govern genome upkeep, cellular growth, and immune surveillance. During the asymptotic persistent period of infection by HOVs, a friable equilibrium to settle this conflict is reached. It is proposed that when this fragile equilibrium is broken, oncogenesis is triggered since the viral tactics that sustain infection start causing uncontrolled proliferation of cells, circumvention of antitumour immunity, and build-up of mutations. The fragile equilibrium can be broken by outside factors that cause immune suppression or damage in the DNA. Endogenous factors can also be responsible, like ageing which is associated with cumulative genetic mutations and suppression of immunity.

Indeed, advanced ageing, host genetic mutations, exposure to certain environmental factors and status of immunity are determinants or co-factors of oncogenesis in hosts harbouring HOVs. For example, cancers induced by EBV, HPV, MCV, KSHV and HTLV-I have an increased incidence in persons who are immuno-suppressed (like patients with AIDS and solid-organ transplants). Also advanced age is a cofactor because it is associated with some immune dysfunction and accumulation of genetic mutations in the host along the years. Furthermore, certain environmental exposures elevate the risk of oncogenesis. For example, mycotoxins, like aflatoxin in food, are connected with HBV-associated hepatocellular carcinoma,[3] and malaria infection is connected with Burkitt's lymphoma in children.[4]

Perturbations of Host Metabolism

Cancer cells often show the 'Warburg effect', whereby cancer cells generate their energy not through the normal Krebs cycle and oxidative phosphorylation in the mitochondria, but through the process of aerobic glycolysis. The latter is less efficient (generates less adenosine triphosphate (ATP)), and occurs in the cytosol.[5] In a similar way, HOVs shift the metabolism of cells, when they infect and transform them.

Adjustments of the Cellular Micro-environment

Human cells that are infected with HOVs and their respective cancer cells are adapted to live in an inhospitable micro-environment, where oxygen is low (hypoxia), pH tends to be acidified, and Warburg metabolism occurs.[6,7] This harsh cellular micro-environment selects these adapted cells over cells which are not infected or not transformed.

One way how hypoxia and the Warburg effect help is by helping these cells escape immune attack.[8,9] For example in EBV infected cells, hypoxia upregulates genes that inhibit interferon production.[10]

In Kaposi's Sarcoma oncogenesis, hypoxia is also fundamental because it activates a cluster of genes which benefit the cells though their modulatory functions.[11,12]

Apoptosis Inhibition

When a virus infects a cell, the innate immunity responds by arresting the cell-cycle and initiates apoptosis.[13] HOVs can inhibit apoptosis via several diverse mechanisms. For example, EBV encodes BHRF1 (BamHI fragment H rightward open reading frame 1) and BALF1 proteins that inhibit Bcl2 (B-cell lymphoma 2) pro-apoptotic factors. EBV also encodes various micro-RNA that inhibit BIM (Bcl-2 Interacting Mediator of cell death) and Puma (p53 upregulated modulator of apoptosis)[14] and this promotes the survival of host cells. Similar strategies are seen with the other HOVs.

Induction of Chronic Inflammation

Chronic inflammation is also blamed as a mechanism of oncogenesis. It is proposed that chronic inflammation causes cells to continuously die and as they are replaced by new cells, these cells over time slowly acquire mutations associated with oncogenesis. It is believed that such chronic inflammation in HBV and HCV induces hepatocellular carcinoma. Similarly chronic inflammation has been proposed as a very important driving force in HPV-related oropharyngeal carcinogenesis.[15]

Epigenetic Perturbations

One of the epigenetic perturbations associated with persistent viral infections is DNA hypermethylation of several viral and cellular genes.[16] This hypermethylation is associated with the formation of condensed heterochromatin and thus the 'switching off' of genes. For example, EBV infection activates DNA methyltransferases that cause hypermethylation of genes that code E-cadherin (epithelial cadherin),[17-19] p16 and p21 (latter two being tumour suppressor genes).[20,21] CDH1 (Cadherin 1) gene codes E-cadherin which is a protein in cell membranes of epithelial cells whose function is to keep these cells adhered together.

Another epigenetic perturbation caused by viral infection is histone epigenetic modification resulting in the remodelling of nucleosomes. For example, HPV infection besides causing DNA hypermethylation also causes post-translational modifications of histone tails. These include histone acetylation, methylation, phosphorylation, sumoylation, and ubiquitination, all impacting on the physical state and the transcriptional state of the chromatin.[22]

Non-coding RNA alterations are also found with persistent viral infections. For example, the long non-coding RNA (lncRNA) HOTAIR (HOX transcript antisense intergenic RNA) is down-regulated in cervical cancer[23] leading to up-regulation of HOXD10(Homeobox D10). Other lncRNAs are discussed in greater detail by Hull et al.[24]

Transcriptional Perturbations

HOVs also target and perturb transcription factors and their networks. For example, p53 and Rb-family complexes of host's cells are perturbed by E6, E7 and T-antigens (viral nuclear factors). Other factors repress tumour suppressor genes, like p16 and BIM (Bcl-2 interacting mediator of cell death).[25]

MEDICAL APPLICATIONS OF RESEARCH ON HOVS

Over the years research and knowledge on oncogenic viruses and viral cancers have been translated into the clinical setting.

Increased Knowledge on Fundamental Cellular Processes

Research on HOVs (and other tumour viruses) has played pivotal roles in the investigation and discovery of many fundamental processes of the cell, like signal transduction, immune regulation, transcriptional enhancers, messenger RNA splicing, and cell cycle control.

Identification of Oncogenes and Tumour Suppressor Genes

Research of virus-induced cancers also revealed the functions of various oncogenes and tumour suppressor genes. Currently and specifically HPV is proving valuable in studies of the epigenome of cancer.

Anti-cancer Vaccines

The fact that viruses could cause cancer was translated into the clinical setting by the development of anti-cancer vaccines, specifically against HPV and HBV. With their advent the incidence of human cancers associated with these viruses has already started to decrease. One might think that similar research-driven knowledge and its clinical application will also prevent and even cure other virus-associated cancers. But unfortunately the transition from bench to clinic for specific viruses faces huge challenges given that the pharmaceutical industry might view the 'relatively low burden' of disease they cause to be not cost-effective.

Antiviral Therapy

Antiviral therapy can be effective in clearing chronic viral infections and so prevent associated cancers. For example, sofosbuvir (a nucleotide analogue inhibitor of HCV NS5B polymerase) is one such effective anti-viral which clears HCV infection and thus prevents hepatocellular carcinoma.[26]

Potential Diagnostic Biomarkers

High performing diagnostic biomarkers can detect cancer at an earlier stage resulting in a better prognosis because of earlier treatment and small cancer burden. Specifically, micro-RNAs (miRNAs) are potential biomarkers in cancers induced by HOVs (Table 2). Indeed, miRNA profiling can differentiate between pathological and physiological states.

Table 2. miRNAs as potential biomarkers of HOVs

HOV	Cancer	miRNA	Level of Expression	Reference
EBV	Nasopharyngeal carcinoma	BART7, 13	Decreased	27
HBV	Hepatocellular carcinoma	miR-885-5p,122,21	Increased	28
HCV	Hepatocellular carcinoma	miR-29a, 146, 149, 221, 222 miR-192a	Increased Decreased	29,30
HPV	Cervical carcinoma	miR-21, 146a, 224, 182 miR-218	Increased Decreased	31-33
MCV	Merkel cell carcinoma	MCV-miR-5p, 23	Decreased	34
KSHV/HHV8	Kaposi sarcoma/B-cell lymphoma	miR-143, 145, 126-3p and 13 miR-221, 222	Increased Decreased	33,35
HTLV-1	T-cell leukaemia	miR-93, 155 miR-126	Increased Decreased	36

Hull et al.[24] also discusses lncRNAs as potential biomarkers and as therapeutic anti-cancer targets. They propose that since lncRNAs expression profile is different as a cancer develops and progresses, it can be used for diagnosis, and to stratify patients vis-a-vis cancer stage and its treatment.

Re-Activation of the Lytic Cycle

Recently, oncolytic viruses have been tested as anti-cancer agents and such interventions are promising. In a similar beneficial way, theoretically, HOVs can be activated into their lytic cycle (thus breaking their latency) and kill the infected cancer cells. Such a reactivation would also mean that viral antigens are generated and this could promote an immune response. Such a conception has spurred research to investigate it.[37] However, it must be pointed out that such reactivation could also mean replication and further spread of the virus.

Re-activating 'Cold' Tumours

Some of the viral tumours are defined as 'cold' (or non-T-cell-inflamed) because there is little or no immune infiltrates in the tumour micro-environment. Viral factors contribute to this diminished immune response. Thus, reinstating an immune activity in such 'cold' tumours is a possible therapeutic approach. Indeed, credence to this principle has resulted in promising achievements in some viral cancers.

A typical example is the successful use of anti-PD1-PDL1 (anti-Programmed cell death protein 1 - Programmed death-ligand 1) immune checkpoint blockade in advanced MCPyV (Merkel cell polyomavirus) associated with MCC (Merkel-cell carcinoma).[38,39] Extrapolating further, if the viral factors that repress immunity are specifically targeted, better targeted immunotherapies can be developed.

ONGOING RESEARCH

Research on human oncogenic viruses is still ongoing. Specifically, it is resolving better the dynamics at the molecular level between the virus and the host during persistent infection and oncogenesis. This promises new therapeutic targets, sensitive biomarkers or prevention strategies. Also, this interest is being extended toother possible HOVs and other tumours that might be virally induced or where the viral infection is a triggering determinant or co-factor. For example, there is already convergent evidence that in cases of long-Covid-19 infections there is long-term suppression of p53 function, the latter being a tumour suppressor. Therefore, this might be itself a trigger to oncogenesis or worsen any already oncogenic processes.[40-42] It has already been shown that SARS-CoV-2 has hijacking strategies that control p53 similar to those used by the EBV and HBV.[43,44] If SARS-CoV-2 is confirmed to be oncogenic, this will definitely and hugely impact negatively on human health into the future.

RESEARCH ON HUMAN ONCOGENIC VIRUSES IS STILL ONGOING. SPECIFICALLY, IT IS RESOLVING BETTER THE DYNAMICS AT THE MOLECULAR LEVEL BETWEEN THE VIRUS AND THE HOST DURING PERSISTENT INFECTION AND ONCOGENESIS

Other viruses are also under scrutiny to see and confirm if they have the status of oncogenic viruses. Known oncogenic viruses are also being incriminated with other carcinomas. In 2022 Afzal et al. identified associations between EBV, HPV and Bovine Leukaemia Virus (BLV) and breast cancer,[45] and between BKPyV (BK Polyoma Virus) and renal cell carcinoma and urothelial carcinoma.[45]

CONCLUSION

Worldwide there is large interest in using -omics to undermine the HOV-host interactions in persistent infection and oncogenesis. Their use is being exploited in identifying viral molecular signatures, biomarkers and dysregulated cellular pathways. Biomarkers that are highly specific would enable clinicians in the theranostic management of cancer caused by these viruses. Specifically, they would aid in cancer theranostics like diagnosis (preferably early) and prognosis. Also, the dysregulated cellular pathways could offer insights of new targets for cancer treatment.

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DR LARA SAMMUT

Personalised Breast Cancer Screening vs One-size-fits-all Approach

INTRODUCTION

Breast cancer is the most common cancer and the leading cause of cancer-related deaths in women worldwide. In 2020, 2.3 million women were diagnosed with breast cancer, with 685,000 deaths registered globally. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer.[1]

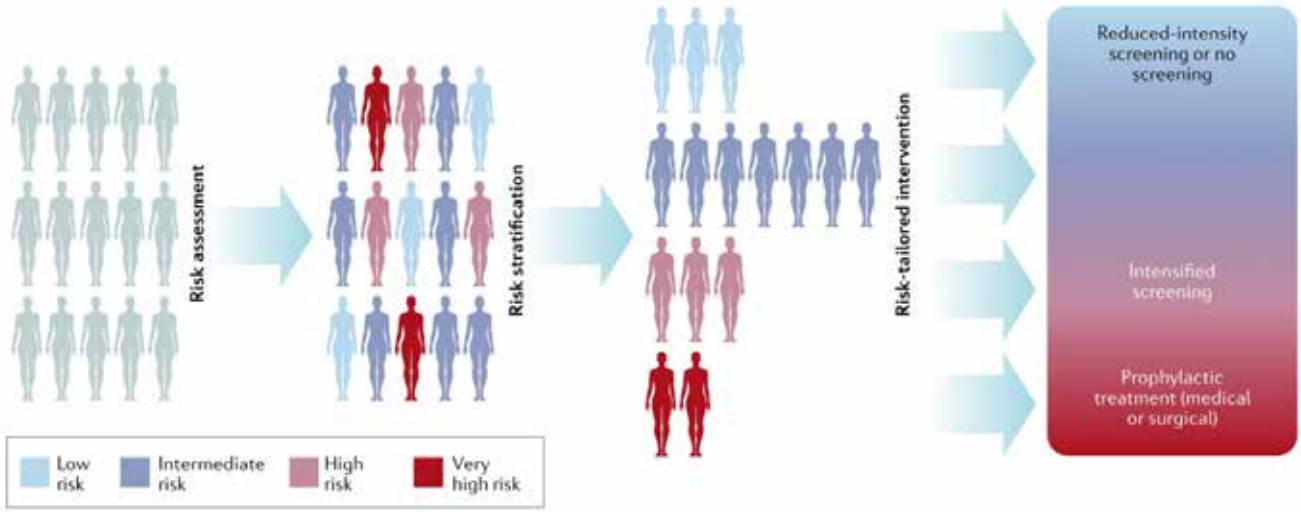
There was little change in breast cancer mortality from the 1930s through to the 1970s when surgery alone was the primary mode of treatment. Improvements in survival began in the 1990s when countries established breast cancer early detection programs together with comprehensive treatment programs including effective medical therapies.[1]

NATIONAL BREAST SCREENING PROGRAMMES

The aim of a National Breast Screening Programme, widely implemented in many healthcare systems, is to reduce breast cancer mortality through the expedited diagnosis of smaller, clinically occult breast cancers. In a meta-analysis of 11 randomised trials, the relative risk of breast cancer mortality for women invited to screening compared with controls was 0.80 (95% CI 0.73–0.89), which is equivalent to a relative risk reduction of 20%.[2]

The Malta National Breast Screening program currently invites women between 50 and 69 years of age for a full field digital 2D mammogram (FFDM) once every two years. During 2022, 11,645 mammograms were performed. Each mammogram is double read by two breast radiologists blindly. If the mammogram is reported as normal by both readers, the patient will be invited for her next mammogram after two years. If only one of the two readers reports a positive finding, the mammogram will be further read by a third reader who then decides whether to recall the patient for further investigations or not. If both readers report a positive finding, the woman is recalled for further investigations such as digital breast tomosynthesis (DBT)/3D mammogram, ultrasound (US), and magnetic resonance imaging (MRI). In some cases, a core biopsy is also performed.

Figure 1. A schematic outlining a personalized approach to early detection and prevention of breast cancer.



Women entering a personalized early detection programme would initially be assessed using a validated tool to determine their estimated risk of breast cancer. Subsequently, the women would be stratified into appropriate risk groups such that they can receive tailored interventions. *Source: Pashayan N, Antoniou AC, Ivanus U et al. Personalized early detection and prevention of breast cancer: ENVISION consensus statement. Nat Rev Clin 2020:687–705.*

Apart from high-risk scenarios such as the presence of highly penetrant genetic mutations, breast screening programs typically comprise mammography or tomosynthesis strategies defined by age alone.[3] But what about other breast cancer risk factors individual women may possess? How can they be assessed and integrated in breast cancer screening programme strategies? How can we shift from a one-size-fits-all approach to personalised risk-stratified screening?

PERSONALISED RISK-STRATIFIED SCREENING

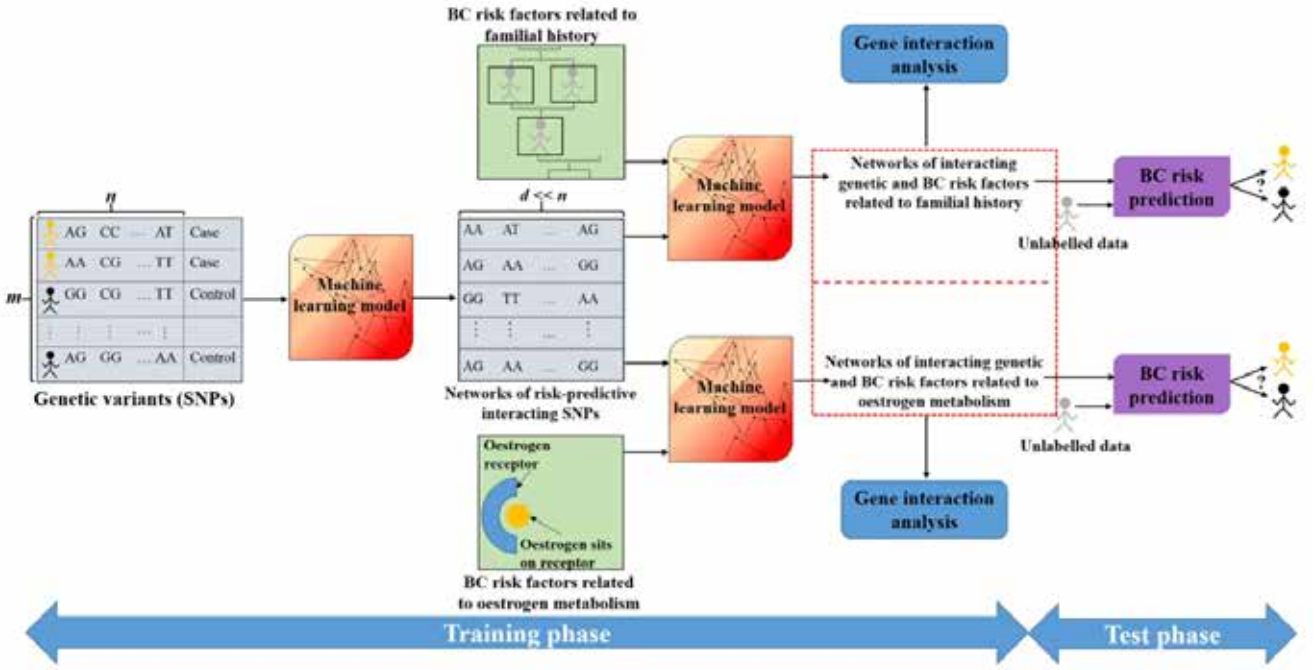
Personalised screening requires an accurate measure of an individual's risk of developing breast cancer. Age, reproductive history, breast density, family history of breast or ovarian cancer, previous benign breast disease, hormonal and lifestyle factors, and a combination of common genetic variants such as single-nucleotide polymorphisms (SNPs) and mutations in the BRCA or other susceptibility genes can be amalgamated to predict breast cancer risk.[4]

This individualised risk assessment would then determine an individualized screening strategy which would include establishing the age of screening initiation and cessation, the screening frequency, the type of screening exam, consideration of preventive treatments for high-risk women, or even decisions regarding the non-screening of low-risk women (Figure 1). In modelling studies, personalised risk-based approaches to the early detection of breast cancer appear to be more efficient and have a better balance of benefits and harms than age-only strategies.[4]

Studies that assess risk estimation, acceptability, feasibility, and the legal and ethical aspects of personalised screening strategies are underway. Two non-inferiority clinical trials comparing risk-based screening with age-based screening - the Women Informed to Screen Depending on Measures of risk (WISDOM) in the USA and My Personal Breast Screening (MyPeBS) in Europe - will complete their respective collections of information by 2025. In Canada, the Personalized Risk Assessment for Prevention and Early Detection of Breast Cancer: Integration and Implementation (PERSPECTIVE I&I) project, and in the United Kingdom, the Predicting the Risk of Cancer at Screening (PROCAS) study, aim to improve personalised risk assessment, perform cost-effectiveness analyses, and identify best practices to implement them in their respective National Health Systems.[4]

In 2019, the European Collaborative on Personalized Early Detection and Prevention of Breast Cancer (ENVISION) organized a consensus conference with international consortia leading the research on personalised breast cancer screening. The consensus statement identified several areas of research that require development to enable evidence-based personalised breast cancer screening and prevention programs. These include breast cancer subtype-specific risk assessment tools and implementation studies addressing feasibility and acceptability combined with modelling studies to evaluate the long-term population outcomes of risk-based screening.[4]

Figure 2. Outline of the proposed breast cancer risk prediction system using Machine Learning.



In the training phase, networks of interacting genetic and demographic risk factors for breast cancer are identified. These networks of features are then used to predict whether an unlabelled individual is a cancer case or a healthy control in the testing phase. This study provides two examples showing that a combination of interacting genetic variants (Single Nucleotide Polymorphisms) with breast cancer risk factors related to both familial history and oestrogen metabolism can increase breast cancer risk prediction accuracy. *Source: Behravan H, Hartikainen JM, Tengström M et al. Predicting breast cancer risk using interacting genetic and demographic factors and machine learning. Sci Rep 2020;10:11044.*

POTENTIAL ROLES OF ARTIFICIAL INTELLIGENCE IN PERSONALISED SCREENING

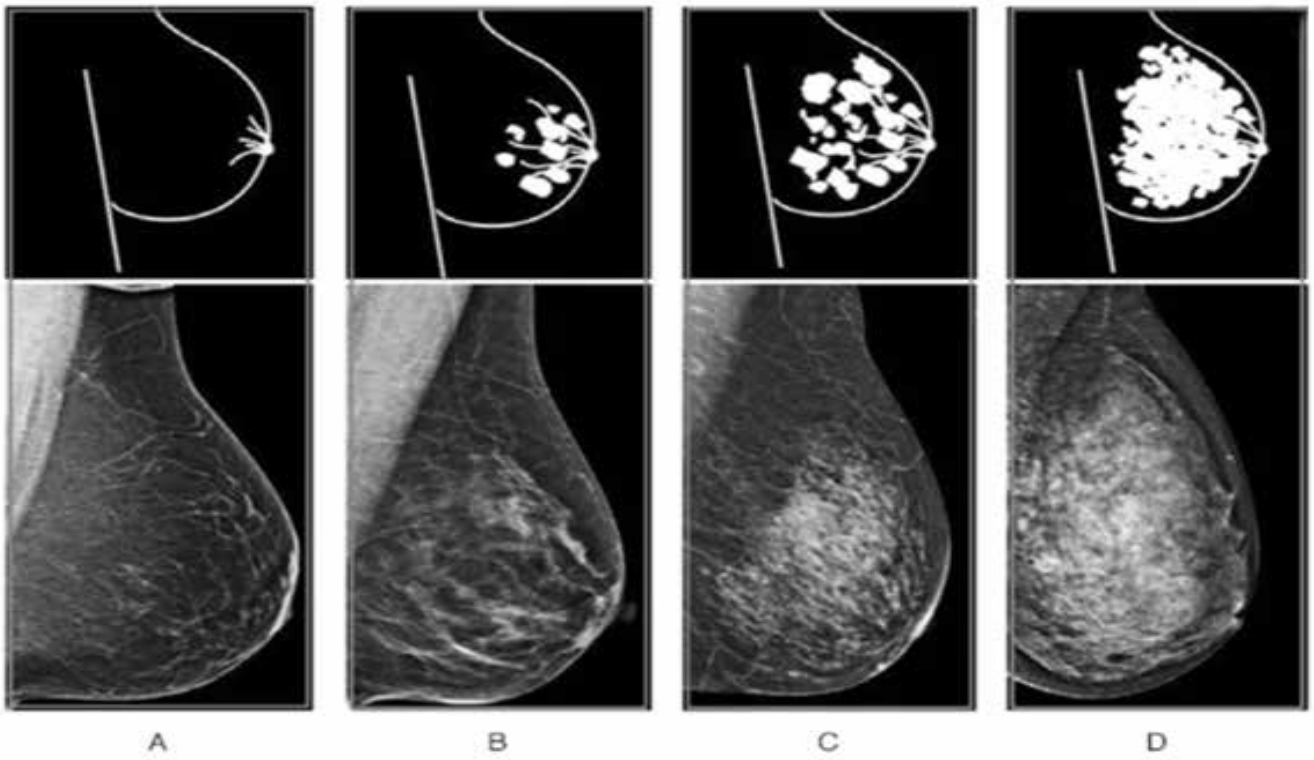
Artificial intelligence (AI) represents a real game changer in breast cancer imaging. Applications include assisted detection of tumour to increase diagnostic accuracy, reducing the rate of false negatives and false recalls, whilst improving radiologist workload; non-invasive tumour characterization (identification of tumour subtype, evaluation of tumour heterogeneity and microenvironment, etc) to plan targeted therapy and follow-up; prognostic/predictive applications regarding response to treatment, risk of relapse and overall survival; and lastly risk stratification, in order to achieve individualized screening programs through AI risk prediction modes (Figure 2).[5]

One of the most popular risk prediction models is the International Breast Intervention Study (IBIS) model, or Tyrer-Cuzick (TC) model, a scoring system guiding breast cancer screening and prevention by accounting for age, genotype, family history of breast cancer, age at menarche and at first birth, menopausal status, atypical hyperplasia, lobular carcinoma *in situ*, height, and body mass index (BMI). Despite its widespread use, however, the IBIS/TC model demonstrated limited accuracy in some high-risk patient populations. AI can help integrate imaging features into predictive risk models increasing accuracy. For example, a study by Yala et al.[6] evaluated the performance of a hybrid deep learning AI model considering both traditional risk factors and mammograms, in comparison with the IBIS/TC model alone: the hybrid model placed 31% of patients in the top risk category, compared with 18% identified by the IBIS/TC model, and was able to identify the features associated with long-term risk beyond early detection of the disease.[7]

SUPPLEMENTAL SCREENING WITH CONTRAST-ENHANCED BREAST MRI FOR WOMEN WITH EXTREMELY DENSE BREASTS

Breast contain glandular tissue, fibrous connective tissue and fat. Breast density is a term used to describe the relative amount of these different tissue types as seen on mammography. The Breast Imaging

Figure 3. Breast density - The four levels.



Reporting and Data System (BI-RADS) classifies breast density into four categories, from A to D, from lowest to highest density.

Category A: entirely fatty breast.

Category B: scattered fibroglandular breast tissue – mostly fatty tissue with some areas of dense glandular and fibrous connective tissue.

Category C: heterogeneously dense breast tissue – many areas of dense glandular and fibrous connective tissue, with some areas of fatty tissue.

Category D: extremely dense breast tissue – breast is almost all dense glandular and fibrous connective tissue [Figure 3].

Women with extremely dense breasts have an increased risk of breast cancer. In addition, cancers in these women are also less likely to be detected on mammography since the sensitivity of mammography decreases with increasing breast density.[8]

Current mammographic screening programs are therefore not enough in this category of women. The results of recent studies, namely the DENSE trial and the EA1411 ECOG-ACRIN study, reporting on contrast-enhanced breast MRI as a screening method in women with extremely dense breasts provide compelling evidence that this cost-effective approach can enable a significant reduction in breast cancer mortality for these women. In light of the available evidence, the **European Society of Breast Imaging (EUSOBI) recommends that women aged 50 to 70 years with extremely dense breasts at average risk, should be offered supplemental screening with contrast-enhanced breast MRI every 2 to 4 years.**[5]

CONCLUSION

Breast cancer imaging continues to evolve and the near future predicts AI-based algorithms for risk-stratification models, moving towards a personalised screening approach.

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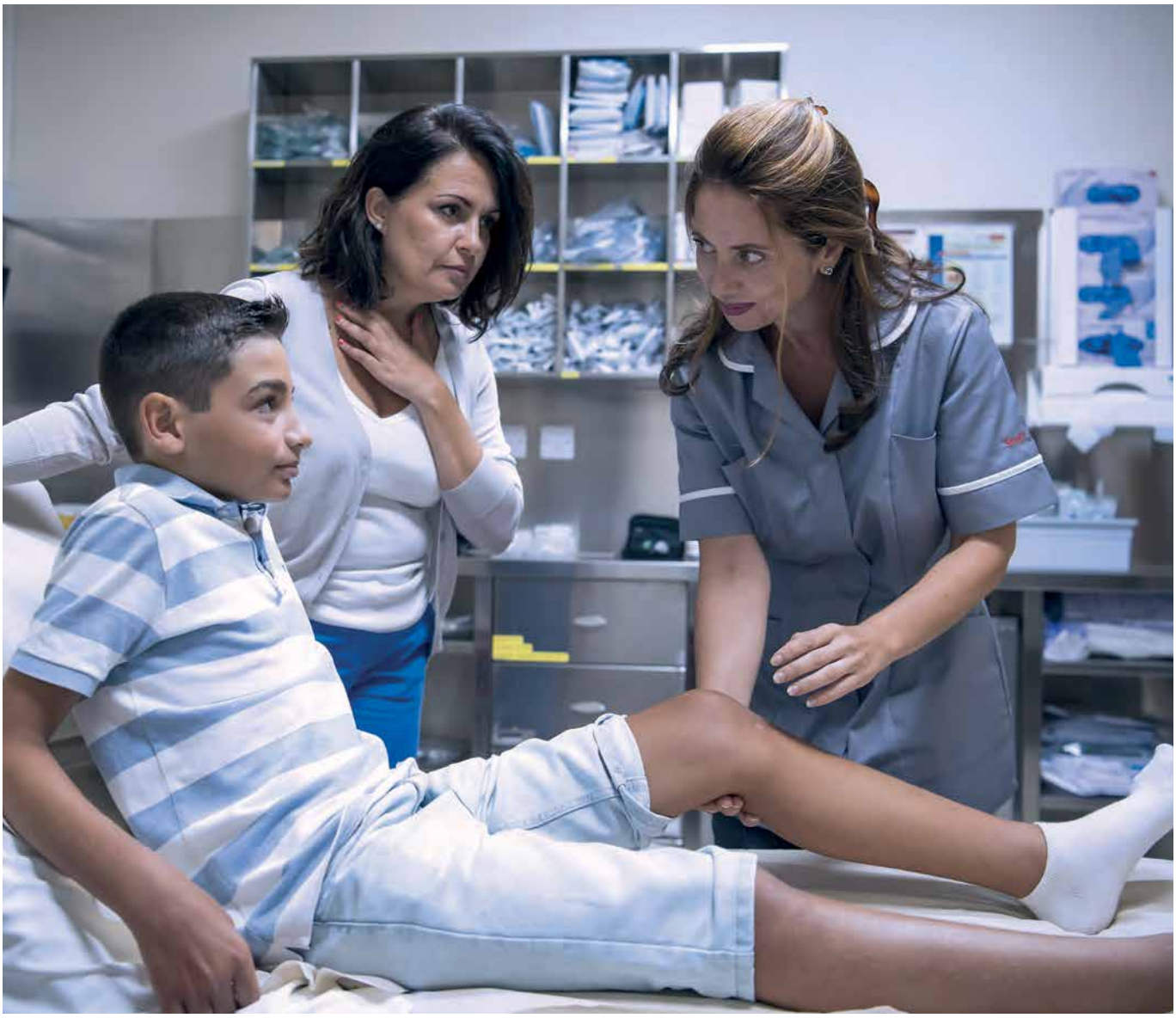

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