VOL 20 2021 ISSUE 01 ISSN NUMBER 2313-8084

thesynapse

THE MEDICAL PROFESSIONALS' NETWORK

Facing Covid

- Ten AI Innovations Disrupting Healthcare
- Meeting Dr Keith Sacco
- Cancer Immunotherapy
- Imaging Tumours of the Ovary

Active Ageing and Community Care Services

a Continuing Medical Education Module for Medical Professionals

Session 1
Community Geriatrician Service
Community Psychogeriatrician Service
Dementia Intervention Team

Session 2
Carer at Home Scheme
Commcare Services
Allied Healthcare Services
Social Work Services

Session 3
Home Help Services
Meals on Wheels
Continence Service
Telecare Service
Phlebotomy Services

Session 4
Respite at Home
Residential Respite
Admission to Residential Care

https://cme30.eu/course/aacc/

Anzjanita' Attiva u Kura fil-Komunita'
Active Ageing & Community Care

cme30.eu
CONTINUING MEDICAL EDUCATION

Authors

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

Prof. Alexiei Dingli B.Sc.IT(Hons)(Melit.) PhD(Sheffield) MBA(Grenoble) is Professor of Artificial Intelligence at the University of Malta.

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-author of the article is Dr Michael Balzan.

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

Issue Guide

TheSynapse

Front Cover:
When 14-year old Rebecca Zammit Lupi was receiving treatment for Ewing's Sarcoma, only her mother Marisa Ford was allowed to stay with her, confined at SAMOC because of Covid-19. During this period, the only way her father Darrin was able to see her was through the slats of the terrace fence overlooking the car park. The front cover depicts the first time Darrin and Rebecca saw each other in three weeks - it took a further four weeks for Darrin to be allowed to switch places with Marisa and get to spend time with his daughter. Rebecca peacefully passed away last January leaving behind her an inspiring legacy of perseverance and tenacity.

Photo Credit: Darrin Zammit Lupi

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

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

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

Production: Outlook Coop

Printing: Europrint Ltd

OUR COLLABORATORS

GMS GERMAN-MALTESE MEDICAL SOCIETY

MMSA Malta Medical Students' Association

MPSA

MADS Malta Association of Dental Students

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

Annual subscription rates outside Malta: Six issues €100 or equivalent, worldwide

NEW SERVICE

Urodynamics

SAINT JAMES HOSPITAL

Solar Blue Urodynamics System

What is Urodynamics?

Urodynamic tests measure the ability of the bladder, sphincters and urethra to store and release urine.

These tests help the physician to better understand and diagnose the cause of the conditions which include:

- urine leakage
- frequent urination
- painful urination
- overactive bladder (urge)
- problems initiating a urine stream
- problems emptying the bladder completely
- recurrent urinary tract infections

info@stjameshospital.com

stjameshospital.com

The Arrow of Apollo

'I swear by Apollo Healer, by Asclepius, by Hygieia, by Panacea, and by all the gods and goddesses, making them my witnesses, that I will carry out, according to my ability and judgment, this oath and this indenture ...'

The above is the beginning of the Hippocratic Oath, taken by all physicians. This traces its origin to Greek mythology where Apollo was revered as the chief god of healing. Nonetheless, his far-reaching arrows could equally inflict epidemics on humankind. For sure, if we were living 2,500 years ago, Covid-19 would have risen through his arrow-heads smeared with this +ve-sense RNA virus.

The International Monetary Fund estimates the pandemic will cost the global economy in excess of $28 trillion in lost output by 2025. Discussing this means sieving through a cornucopia of reasons including lockdown measures, reduction of future earnings for students affected by schools' closure, share of tourism on one's economy, quality of governance … the list goes on. Regretfully, any initial attempts to seed trans-continental cooperation were undermined by distrust. Suffice it to mention the resolution pushed in 2020 by the EU and Australia calling for a review into the Chinese origins of Covid-19 and ensuing delays in alerting the international community on this disease. Against this backdrop we are still experiencing the laissez-faire attitude of nincompoops the world over which has contributed no small part to the spread of this virus, especially to the elderly, vulnerable, as well as front-liners.

In stark contrast, the raw and harsh realities faced by families are aptly embodied by the heart-rendering image on our cover page, captured by Darrin Zammit Lupi. His daughter Rebecca, or Becs as she was affectionately called, has since left us. Zammit Lupi's rendering illustrates the universality of the manner in which Covid-19 has made living life a gargantuan challenge for sick people. Those actions which we invariably took for granted are those which are most sorely missed… holding hands, capturing the smell of the skin, or seeing one's reflection in the eyes of our loved ones, especially the elderly and sick relatives …

In the midst of this discordance, science has struggled to prevail, first through the advice conveyed by public health specialists and then through pre-clinical and clinical studies. We now have a better understanding of this virus. In keeping with this, we are also better equipped with the necessary armamentarium. The challenges which invariably present themselves, although foreseen, corroborate the need to share knowledge and form partnerships between different stakeholders. These challenges range from new variants to logistics relating to vaccine administration. Still, only a few weeks ago we saw the president of the European Commission, Ursula Von der Leyen, admitting that the EU "underestimated the difficulties of mass production [of vaccines]" and that "mistakes were made". A far cry from her "European success story" trumpeted in December.

By this stage we all know that politics and public health are uncomfortable bedfellows. Walking the tightrope of wealth and health is not easy and being armchair critics is easy enough for most of us. I will not delve on the issues stemming from lockdowns but indeed, many countries are now taking off from the backburner important discussions relating to economic growth measurements. This change of heart has picked up momentum during the pandemic. Similarly, such discussions are percolating in the echelons of the Maltese parliament. Of note is the doughnut economic model - alluded to during my recent interviews with two public health trailblazers residing abroad, Prof. Sandro Galea in the US & Prof. Claire Gerada in the UK - departing from the conservative 'GDP', which considers other important variables such as wellbeing indexes.

O Brave New World!

Ian Ellul

Speaking Truth to Politics

After meeting Prof. Sandro Galea and Prof. Claire Gerada, we continue with our series of interviews with Maltese medics residing abroad. In this case, how did a young medical graduate from Żurrieq end up working alongside Dr Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases? Dr Ian Ellul catches up with **Dr Keith Sacco**, who works in the immunology field.

YOUR FATHER, DR RAY SACCO, HAS A BUSY PRACTICE IN ŻURRIEQ. AFTER GRADUATING, THE EASIEST OPTION FOR YOU WOULD HAVE BEEN TO JOIN HIS PRACTICE. NONETHELESS, IN 2015 AFTER YOUR HOUSEMANSHIP ENDED, YOU LITERALLY PACKED AND TRAVELLED TO THE MAYO CLINIC IN FLORIDA. HOW COME?

During my undergraduate years I reflected on the specialty which I was most passionate about and came to realize that it was immunology. In keeping with this, I was repeatedly advised that going to the US would be the wisest option since it would add value to such specialization. I thus took the leap and moved to the Mayo Clinic; its excellent clinical care proved to be an excellent launch pad for me.

BACK IN MALTA YOU WERE MUSICAL DIRECTOR OF THE ŻURRIEQ COUNCIL BAND, WHICH POSSIBLY STEMS FROM YOUR PASSION FOR EVERYTHING WHICH IS RELATED TO YOUR HOMETOWN. WAS IT DIFFICULT TO ADAPT TO THE US CULTURE?

I was socially engaged in Malta. I also formed part of the National Youth Orchestra. This yielded important cultural twinning opportunities which proved valuable since I got to meet people from all walks of life and learnt to adapt to their way of thinking. This was further strengthened through my participation in exchanges during my undergraduate years. Nonetheless, I admit that I faced a different culture in the US which contrasted greatly with the Maltese general laid-back attitude; the first few months proved to be a steep learning curve. The fact that few Maltese physicians reside in the US did not help much; I had no reference points to turn to. It would have been nice to draw from such experience. Suffice it to say that the last Maltese medic to venture here did so over ten years ago.

HOW DID YOU END UP AT THE NATIONAL INSTITUTES OF HEALTH, IN BETHESDA, IN 2018?

The US Department of Health includes the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA) and National Institutes of Health (NIH). The NIH is the primary agency of the US government responsible for biomedical *and* public health research. It has 27 institutes. 90% of NIH funding goes to extramural activities and 10% goes to intramural institutes (such as the main campus in Bethesda, which is within the Washington D.C. metropolitan area).

During my work experience at the Mayo Clinic I strengthened my conviction of specializing in immunology and it became increasingly evident that the NIH was the place to be. I was offered a fellowship (which is equivalent to the last few years of HST training in Malta) and moved there. It is a privilege to work at he NIH; suffice it to say that the NIH saw the first trials of chemotherapy as well as gene therapy in the world.

IS YOUR WORK CLINICAL OR MORE RESEARCH-BASED?

I mainly work at the NIH Clinical Centre which is on the intramural NIH campus in Bethesda, Maryland. This centre is the largest hospital in the US dedicated solely for clinical research. I see patients and carry out clinical work relating to research protocols. In order to get more clinical experience fellows also have the opportunity to go to the John Hopkins in Baltimore, as well as other hospitals. During my protected research time I then work at the National Institute of Allergy and Infectious Diseases (NIAID) which is one of the NIH's institutes. At the NIAID I carry out research on patient samples and also carry out pre-clinical animal modelling.

WE HEARD A LOT ON DR FAUCI, THE DIRECTOR OF THE NIAID SINCE 1984. INDEED, IF WE INCLUDE JOE BIDEN, HE ADVISED SEVEN US PRESIDENTS ON PUBLIC HEALTH ISSUES. DESCRIBE YOUR WORK EXPERIENCE, WITHIN THE NIH, UNDER THE ADMINISTRATION OF TRUMP.

On Monday, Wednesday and Friday the principal investigators carry out ward rounds (like the British system) and we fellows are like the consultants on the service, where we have the patients presented to us by the residents. Dr Fauci still sees patients during his monthly ward rounds. He invariably speaks to us on a first name basis whenever we seek assistance from him in relation to specific cases.

As explained, the NIH has a lot of institutes. The biggest is the National Cancer Institute. When Dr Fauci started in 1984 the NIAID was the 5th largest institute in terms of funding ($319.6 million). Through his career, it is now the 2nd largest ($4.7 billion government funds in 2020). Returning to your question relating to the Trump administration, his advice to us has always been to 'Speak truth to power'.

MOVING ON TO MORE TECHNICAL ISSUES, WHAT ARE YOUR VIEWS ON INTEGRATIVE OMNICS, INCLUDING THE MICROBIOME, IN ALLERGIES?

Our interaction with the microbiome is increasingly being placed in the limelight. We know that babies born via cesarean delivery

are at a higher risk of eczema because their skin does not receive the optimal microbial diversity during delivery through the vaginal canal. Also, infants who receive antibiotics early on, have a diminished microbiome diversity. In keeping with this, studies conducted by Dr Yasmine Belkaid, Director of the Metaorganism Immunity Section at the NIH, have demonstrated that certain species of bacteria grow in areas of eczema flares; this is due to a change in skin microbiota. Preliminary results have indeed shown that when specific microbes are topically transplanted to the affected area with a view to take over, the inflammation decreases.

WHAT ARE YOUR VIEWS ON AI AND MACHINE LEARNING?

The way we conduct research has not changed much along the years; we ask a question and we conduct experiments to validate a hypothesis. Through omics we now have access to big data, which is more than we can interpret. AI and machine learning are proving to be of great value in clinical work through their ability to integrate different data quickly.

One must appreciate that immunology-related data revolves around blood measurements, but many changes occur at the tissue level; one cannot simply conduct biopsies on a regular basis to validate a specific hypothesis, of course. AI together with computer modelling have an important role there.

Our microbiome changes in space and time. A person's microbiome in Malta will be different from that person's microbiome residing in the US. Circadian rhythms as well as psychosocial stress affect it as well. Through AI we can incorporate various variables in time and space to understand better such changes.

HAVE THERE BEEN RECENT DEVELOPMENTS ON THE ROLE OF BIOMARKERS IN ALLERGY?

Biomarkers are classically defined as measures which highlight specific changes in the biology of an organism. Allergologists and immunologists were among the first specialties to promote personalised medicine, since biomarkers guide us to the mechanism of the disease. Taking asthma as an example, when patients are not adequately controlled with high-dose inhaled corticosteroids and long-acting beta agonists, immunologists use biologics e.g. omalizumab. Omalizumab is an anti-IgE high-affinity monoclonal antibody. The biomarkers required to prescribe this are a high IgE together with evidence, through blood or skin testing, for sensitivity to perennial allergens such as dust mites. These two measures are biomarkers. Other biologics include anti-IL5 monoclonal antibodies such as mepolizumab, reslizumab and benralizumab which block either IL-5 or IL-5 receptors. Eosinophils thrive on IL-5 and these play an important role in allergic asthma. For these biologics you need to have 150-300 eosinophils/μL in peripheral blood.

WHAT ARE THE BENEFITS OF IMMUNOSTIMULATION VIS-À-VIS INFLAMMAGING IN OLDER ADULTS? I AM SPECIFICALLY REFERRING HERE TO MICRONUTRIENTS SUCH AS VITAMIN D.

In the Western world people tend to have more exhausted T cells. I like to draw the analogy of a broken car going uphill, which produces more fumes. Exhausted T cells are pro-inflammatory and this seems to stem from overfeeding and a general lack of rest. Indeed, observational studies have shown that shift workers, who work regular night shifts have a higher relative risk of developing cancer, probably due to sleep deprivation. In fact the International Agency for Research on Cancer (IARC) classified night shift work as "probably carcinogenic to humans" based on limited research evidence. On the other hand, a daily fasting period of 10-12 hours - which allows the liver to rest and switch to glycogenolysis and gluconeogenesis – seems to decrease such inflammation and ensuing insulin resistance. These closely related mechanisms share common factors such as increased IL-6 and CRP. Another related concept is autophagy which is one way to maintain cell homeostasis and could prevent development of dysplasia. Animal models have shown that a low-fat diet, with adequate fasting times and good sleep hygiene tend to promote autophagy.

Returning to your question, population-based studies indicate that for specific skin diseases a low vitamin D seems to predispose to a Th9 cell-type of inflammation which is similar to what we see in psoriasis (albeit this is a Th17 type of inflammation). Adequate serum vitamin D levels of 30-50nmol/L maintain an adequate skin keratinocyte turnover. This, of course, is not absolute. I personally do not advice patients to stop anything which does not cause overt harm, to avoid jeopardising the doctor-patient relationship. Notwithstanding this, I would not advise them to start any micronutrients unless I am absolutely sure of their benefit.

HOW DO YOU SEE YOURSELF IN TEN YEARS' TIME? BACK IN MALTA OR IN OTHER GREENER PASTURES?

I would never have imagined myself here ten years ago. However, my compass today is always directed to places where I can provide value to others. At the Mayo clinic I have been taught that if I am resourceful to others, opportunities will invariably come along. I am fortunate enough that immunology is a very dynamic and cellular science and thus will always keep up with the times. Most probably in ten years' time we would be dealing with other medical agendas. What I can say is that personally, geography is not a decision factor and I am open to any opportunity which may present itself.

WHAT DO YOU THINK OF OUR ONLINE CONTINUOUS MEDICAL EDUCATION PLATFORM CME.30?

CME.30 proves to be an excellent rendition of topical medical discussions aimed at healthcare professionals. It is a trailblazing initiative from your part and the reader engagement is behemont. The Covid-19 online symposium which you organized had over 600 participants. Unfortunately medical expertise is not valued much on social media so **CME.30** is the perfect tool for us physicians to discuss ideas with peers, update our learning and, in keeping with this, continue to uphold the values outlined in the Hippocratic oath.

The views and opinions expressed in this interview are solely of the interviewee and do not necessarily reflect the official policy or position of the US National Institutes of Health or the US government.

DR ALFRED GRECH & DR MICHAEL BALZAN

Cancer Immunotherapy

ABSTRACT

Cancer immunotherapy employs the immune system of the human body to fight and kill cancerous cells. This review article explores the translational research in immunotherapy that is revolutionising cancer treatment, including the use of cancer vaccines, checkpoint inhibitors, chimeric antigen receptor T-cells, cytokines and monoclonal antibodies.

INTRODUCTION

The immune system rests on two pillars: the innate, general immune system and the adaptive, specialised immune system. Both systems work together but carry out different tasks.The main aim of the innate immune response is to instantly prevent the spread of foreign pathogens, or germs, throughout the body. If the innate immune system is ineffective in destroying these pathogens, the adaptive immune response sets in – this is specific to the pathogen presented.

Many tumours are recognised as foreign by the adaptive immune system. However, this response can be inhibited by immunosuppressive mechanisms within the tumour, which is why patients do not always achieve long-term responses to existing immunotherapies. Cancer immunotherapy, also known as immuno-oncology, is a type of cancer treatment that uses the immune system to prevent, control and eliminate cancer. It can be used in combination with chemotherapy, radiation, surgery or targeted therapies to increase their efficiency. Cancer immunotherapy comes in many forms, including cancer vaccines, checkpoint inhibitors, chimeric antigen receptor T-cell therapy, cytokines and monoclonal antibodies.[1]

TYPES OF CANCER IMMUNOTHERAPY

Cancer Vaccines

Over the years, researchers have been looking at vaccines as a potential treatment for cancer. Similar to how vaccines work against other diseases, cancer vaccines are designed to recognise proteins on specific cancer cells. In turn, this helps the immune system to recognise and attack those cancer cells. Currently, there are four vaccines approved by the U.S. Food and Drug Administration (FDA) that can help prevent cancer, as well as two others for the treatment of cancer.

Preventive Cancer Vaccines

It is established that viral infections are to blame for the development of many cancers, and in fact, preventive vaccines have been found to play a significant role in reducing the risk. For example, cervical and head and neck cancers can be caused by the human papilloma virus (HPV), whereas liver cancer can be triggered by the hepatitis B virus (HBV). In light of this, numerous vaccines have been developed that can prevent HBV and HPV infection and, consequently, protect against HBV- and HPV-related cancers.

Cervarix®, for instance, is an FDA-approved vaccine used in preventing infection by the two strains of HPV that cause the most cervical cancers: HPV types 16 and 18.[2] Similarly, the Gardasil® vaccine prevents infection by HPV types 6, 11, 16, and 18, whereas Gardasil-9® prevents infection by HPV types 16, 18, 31, 33, 45, 52, and 58, and also prevents genital warts caused by HPV types 6 or 11.[3,4] Overall, all 3 vaccines can help prevent the development of HPV-related anal, cervical, head and neck, penile, vaginal, and vulvar cancers. In regard to the hepatitis B virus, HEPLISAV-B® is a vaccine that protects against infection by HBV and so helps in the prevention of HBV-related liver cancer.[5]

Therapeutic Cancer Vaccines

Nowadays, it is possible to identify targets on apatient's tumour that can help distinguish cancer cells from normal cells. Often, these targets are normal proteins produced at abnormal levels by cancer cells, such as prostatic acid phosphatase for example, which is often overexpressed by prostate cancer cells. By using this information, researchers have been able to develop vaccines such

as the FDA-approved Sipuleucel-T (Provenge®) vaccine which is used for the treatment of patients with advanced prostate cancer.[6] The European Medicine Agency have also approved in 2016 a vaccine (PDX-Survivac) that targets survivin, which is a protein that is over-expressed on ovarian cancer cells preventing their death.[7]

PDX-Survivac is also in a phase 2 clinical trial (ClinicalTrials.gov Identifier: NCT03836352) where subjects with advanced and recurrent solid tumours have been enrolled. The tumours include ovarian cancer, hepatocellular carcinoma, non-small cell lung cancer, and bladder cancer.

Along similar lines, Ambler et al.[8], at the Francis Crick Institute, London, UK, have designed a KRAS neoantigen peptide vaccine. KRAS is a gene that when it mutates makes cells to become cancerous. This mutation is present in many types of lung, bowel and pancreatic cancers. Promising results on mice speared clinical trials of this vaccine (ClinicalTrials.gov Identifier: NCT04117087).

The Bacillus Calmette-Guérin (or BCG) vaccine is another therapeutic cancer vaccine, used to treat early-stage bladder cancer. Specifically, it is a tuberculosis vaccine that uses weakened bacteria to fuel the immune system. In 1990, it became the first immunotherapy to be approved by the FDA.[9] Thirty years later, the search continues, and in fact, other cancer vaccine targets are currently being evaluated in clinical trials, including 5T4-, p53- and telomerase-based cancer immunotherapy.[10,11,12] Oncolytic viruses are also being designed and used for cancer immunotherapy. In fact the first oncolytic virus (OV) to treat metastatic melanoma have been approved.[13] Specifically, in the field of cancer virotherapy, OV can be armed with transgenes to increase their ability to kill cancer cells and leave normal cells unharmed.

Checkpoint Inhibitors

Immune checkpoints are proteins on immune cells that need to be activated or inactivated to elicit an immune response. Sometimes, cancer cells use these checkpoints to avoid attack by the immune system. Checkpoint inhibitor drugs are used to target these checkpoints, which therefore makes them a promising new avenue for cancer treatment. Two types of checkpoint inhibitor drugs are those that target the checkpoint proteins PD-1 or PD-L1 (programmed death ligand 1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) on T-cells.[14]

Examples of FDA-approved antibody drugs that target PD-1 include Cemiplimab (Libtayo®), Nivolumab (Opdivo®) and Pembrolizumab (Keytruda®). Examples of drugs that target PD-L1 include Atezolizumab (Tecentriq®), Avelumab (Bavencio®) and Durvalumab (Imfinzi®). Overall, these drugs have been significant in treating different types of cancer, from advanced cutaneous squamous-cell carcinoma[15] to non-small-cell lung cancer.[16] Also, Ipilimumab (Yervoy®), which targets CTLA-4, is used to treat melanoma of the skin and continues to be tested for other cancers as well.[17]

Chimeric Antigen Receptor T-Cell Therapy

Adoptive cell transfer (ACT) is an immunotherapy approach where a patient's own immune cells are collected and used to treat their cancer. Several types of ACT exist, but, CAR T-cell therapy is the most advanced in terms of clinical development. In CAR T-cell therapy, T-cells are taken from a patient's blood and then engineered so as to attack cancer cells. Specifically, the gene for a chimeric antigen receptor that binds to a protein on the patient's cancer cells is added. In the end, large quantities of the CAR T-cells are grown in the lab and given to the patient by infusion.

The use of CAR T-cell therapy has, until recently, been limited to small clinical trials. However, in 2017, two CAR T-cell therapies were approved by the FDA: Tisagenlecleucel (Kymriah®) for the treatment of acute lymphoblastic leukaemia[18] and Axicabtagene ciloleucel (Yescarta®) for advanced lymphomas.[19]

Cytokines

Cytokines such as interferon and interleukin are a group of proteins that play a central role in boosting the immune system. Over the years, researchers have created man-made versions of these to treat cancer. For example, interferon is used for different types of cancer including kidney cancer, melanoma, multiple myeloma and a few types of leukaemia. Similarly, interleukin is used to treat kidney cancer, although it is also in clinical trials for other types of cancer.[20]

Monoclonal Antibodies

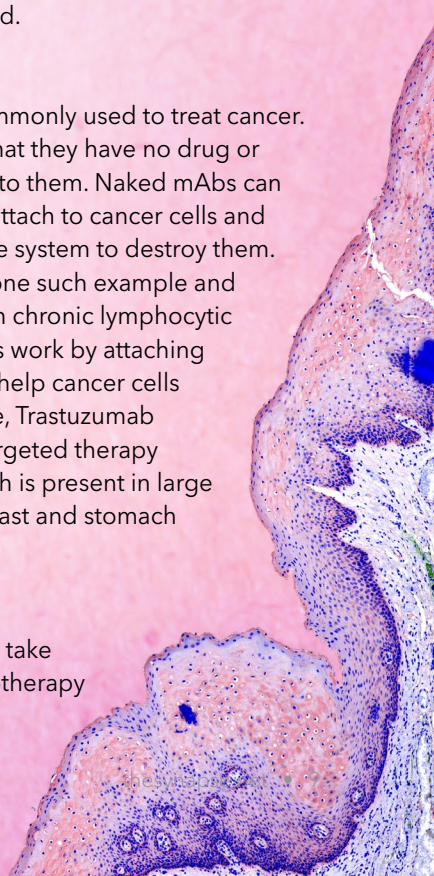
Monoclonal antibodies (mAbs) are artificial versions of immune system proteins. Since they can be designed to attack definite parts of a cancer cell, mAbs can be useful in treating cancer. mAbs used to treat cancer can be bispecific, conjugated or naked.

Naked mAbs

Naked mAbs are the most commonly used to treat cancer. They work by themselves, in that they have no drug or radioactive particles attached to them. Naked mAbs can work in different ways. Some attach to cancer cells and act as a marker for the immune system to destroy them. Alemtuzumab (Campath®) is one such example and is used to treat individuals with chronic lymphocytic leukemia.[21] Other naked mAbs work by attaching to and blocking antigens that help cancer cells grow and spread. For example, Trastuzumab (Herceptin®) is an antibody-targeted therapy against the HER2 protein which is present in large amounts on the surface of breast and stomach cancer cells.[22]

Conjugated mAbs

Conjugated mAbs are used to take radioactive particles or chemotherapy drugs directly to cancer cells.



Specifically, these mAbs circulate around the body until they find and hook onto the target antigen. As such, the toxic substance is delivered where it is needed the most, which decreases the damage to normal cells in other parts. An example of a radiolabelled mAb is Yttrium-90-Ibritumomab Tiuxetan (Zevalin®) which is used in patients with relapsed follicular non-Hodgkin lymphoma.[23] Similarly, the chemolabelled mAb Brentuximab vedotin (Adcetris®) has shown remarkable efficacy in CD30-positive lymphomas, such as Hodgkin's lymphoma and systemic anaplastic large-cell lymphoma.[24]

Bispecific mAbs

Bispecific mAbs are composed of parts of two different mAbs, that is, they can attach to two different proteins at the same time. An example is Blinatumomab (Blincyto®), used to treat some types of leukemia, where one part attaches to the CD19 protein found on some leukemia and lymphoma cells, and the other part attaches to the CD3 protein found on T- cells. By binding to both CD3 and CD19 proteins, Blinatumomab is able to bring both the cancer cells and immune cells together, which is meant to elicit the immune system to attack the cancer cells.[25]

SIDE EFFECTS OF IMMUNOTHERAPY

In general, the side effects of immunotherapy are different from those seen with conventional treatments. This is because they result from a misdirected or overstimulated immune response rather than the effects of chemical or radiological therapy. Overall, the side effects of immunotherapy vary depending on the treatment type, as well as the location, type of cancer and the patient's overall health. In principle, immune-related side effects can have an effect on any tissue or organ, and can range from mild and moderate to severe becoming life-threatening under particular circumstances.[26,27] In most cases, however, immunotherapy-related side effects can be managed with immunosuppressive drugs such as steroids as long as they are addressed early.

CONCLUSION

In the last few decades, immunotherapy has become central in treating different types of cancer, so much so that new ways of working with the immune system are constantly being discovered. Epigenetic research, for instance, is showing that there is the potential to combine epigenetic drugs with immunotherapeutic agents.[28] Similarly, it has been found that the role of the microbiome in controlling the immune response is essential and therefore also significant in cancer immunotherapy. Indeed, research is already ongoing to find out how to modulate the microbiome and enhance the immunotherapeutic effect when treating cancer.[29] Translational research in cancer immunotherapy is in hyper drive and will provide other possibilities in the fight against cancer.

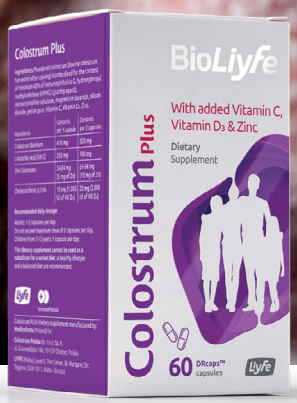
REFERENCES

1. Dougan M, Dranoff G, Dougan SK. Cancer Immunotherapy: Beyond Checkpoint Blockade. *Annual Review of Cancer Biology* 2019;3(1):55-75.
2. Monie A, Hung C-F, Roden R, et al. Cervarix: a vaccine for the prevention of HPV 16, 18-associated cervical cancer. *Biologics* 2008;2(1):97-105.
3. McLemore MR. Gardasil: Introducing the new human papillomavirus vaccine. *Clinical Journal of Oncology Nursing* 2006;10(5):559-60.
4. Kirby T. FDA approves new upgraded Gardasil 9. *The Lancet Oncology* 2015;16(2):e56.
5. Splawn LM, Bailey CA, Medina JP, et al. Heplisav-B vaccination for the prevention of hepatitis B virus infection in adults in the United States. *Drugs of Today* 2018;54(7):399-405.
6. Gardner TA, Elzey BD, Hahn NM. Sipuleucel-T (Provenge) autologous vaccine approved for treatment of men with asymptomatic or minimally symptomatic castrate-resistant metastatic prostate cancer. *Human Vaccines &Immunotherapeutics* 2012;8(4):534-9.
7. European Medicines Agency. Public summary of opinion on orphan designation. *EMA/686282/2016* (as on https://bit.ly/3390qLP).
8. Ambler R, Von Karstedt S, Downward J. Targeting a KRAS neoantigen peptide vaccine to DNGR-1+ dendritic cells. *ENA 2020* (Session title: Late Breaking and Best Proffered Papers).
9. Guallar-Garrido S, Julián E. Bacillus Calmette-Guérin (BCG) Therapy for Bladder Cancer: An Update. *Immunotargets Ther* 2020;9:1-11.
10. Stern PL, Harrop R. 5T4 oncofoetal antigen: an attractive target for immune intervention in cancer. *Cancer Immunol Immunother*2017;66(4):415-26.
11. DeLeo AB, Appella E. The p53 Saga: Early Steps in the Development of Tumor Immunotherapy. *Journal of Immunology* 2020;204(9):2321-8.
12. Kailashiya C, Sharma HB, Kailashiya J. Telomerase based anticancer immunotherapy and vaccines approaches. *Vaccine* 2017;35(43):5768-75.
13. Ylösmäki E, Cerullo V. Design and application of oncolytic viruses for cancer immunotherapy. *Curr Opin Biotechnol* 2020; 65:25-36.
14. Lee HT, Lee SH, Heo YS. Molecular Interactions of Antibody Drugs Targeting PD-1, PD-L1, and CTLA-4 in Immuno-Oncology. *Molecules*2019;24(6).
15. Migden MR, Rischin D, Schmults CD, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. *The New England Journal of Medicine* 2018;379(4):341-51.
16. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *The New England Journal of Medicine* 2017;377(20):1919-29.
17. Graziani G, Tentori L, Navarra P. Ipilimumab: a novel immunostimulatory monoclonal antibody for the treatment of cancer. *Pharmacological Research* 2012;65(1):9-22.
18. Liu Y, Chen X, Han W, et al. Tisagenlecleucel, an approved anti-CD19 chimeric antigen receptor T-cell therapy for the treatment of leukemia. *Drugs of Today*2017;53(11):597-608.
19. Jain MD, Bachmeier CA, Phuoc VH, et al. Axicabtagene ciloleucel (KTE-C19), an anti-CD19 CAR T therapy for the treatment of relapsed/refractory aggressive B-cell non-Hodgkin's lymphoma. *Ther Clin Risk Manag* 2018;14:1007-17.
20. Berraondo P, Sanmamed MF, Ochoa MC, et al. Cytokines in clinical cancer immunotherapy. *British Journal of Cancer* 2019;120(1):6-15.
21. Osterborg A, Mellstedt H, Keating M. Clinical effects of alemtuzumab (Campath-1H) in B-cell chronic lymphocytic leukemia. *Medical Oncology* 2002;19 Suppl:S21-6.
22. Wilson FR, Coombes ME, Brezden-Masley C, et al. Herceptin® (trastuzumab) in HER2-positive early breast cancer: a systematic review and cumulative network meta-analysis. *Syst Rev* 2018;7(1):191.
23. Puvvada SD, Guillen-Rodriguez JM, Yan J, et al. Yttrium-90-Ibritumomab Tiuxetan (Zevalin(R)) Radioimmunotherapy after Cytoreduction with ESHAP Chemotherapy in Patients with Relapsed Follicular Non-Hodgkin Lymphoma: Final Results of a Phase II Study. *Oncology* 2018;94(5):274-80.
24. Yi JH, Kim SJ, Kim WS. Brentuximab vedotin: clinical updates and practical guidance. *Blood Res* 2017;52(4):243-53.
25. Hathaway L, Sen JM, Keng M. Impact of blinatumomab on patient outcomes in relapsed/refractory acute lymphoblastic leukemia: evidence to date. *Patient Relat Outcome Meas* 2018;9:329-37.
26. Hoffner B, Zitella LJ. Managing Side Effects of Cancer Patients Treated With Immunotherapy. *J Adv Pract Oncol* 2018;9(3):287-92.
27. Abdel-Wahab N, Alshawa A, Suarez-Almazor ME. Adverse Events in Cancer Immunotherapy. *Advances in Experimental Medicine And Biology* 2017;995:155-74.
28. Dunn J, Rao S. Epigenetics and immunotherapy: The current state of play. *Molecular Immunology* 2017;87:227-39.
29. Gopalakrishnan V, Helmink BA, Spencer CN, et al. The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy. *Cancer Cell* 2018;33(4):570-80.

BioLiyfe

For a strong & healthy immune system

Colostrum



Each capsule of **Colostrum Max** has a high amount (410 mg) of pure colostrum bovinum that contains **IgG (40%), IgA, IgM and Lactoferrin.**

Each capsule of **Colostrum Plus** has a high amount (410 mg) of pure colostrum bovinum that contains **IgG (40%), IgA, IgM, Lactoferrin and with additional Vitamin C, Vitamin D3 and Zinc.**

Liyfe

Marketed & distributed by **PAC 3 Ltd.** For more information please visit **www.pac3.eu/products/colostrum-max** or contact Rachel Grech on **(+356) 9942 9974** or Email **rachel.grech@pac3.eu**

PAC3

ACCU-CHEK® Guide

Roche

DAILY SUPPORT.

PURE AND SIMPLE.

and easy every time with the Accu-Chek Guide system.

UPGRADE TODAY

Connects with

mySugr

Available from all leading pharmacies

PROF. ALBERT CILIA-VINCENTI

Phenotyping Prediabetes

Prediabetes, defined by an HbA1c ranging from 5.7% to 6.4%, may be accompanied by an increased risk of complications before progression to overt diabetes type 2. This early pathophysiological dysregulation often remains undiagnosed. Recent studies are claiming different phenotypes of prediabetes.

One such study published in *Nature Medicine*[1] describes six pathophysiological phenotypic clusters using the oral glucose tolerance test (OGTT), fasting insulin, triglycerides (TRGs), HDL cholesterol, MRI-measured visceral and subcutaneous fat, liver fat assessed with H-MR spectroscopy, and a polygenic risk score for type 2 diabetes. Carotid intima thickness (IMT) was also measured together with pancreatic and renal hilar fat.

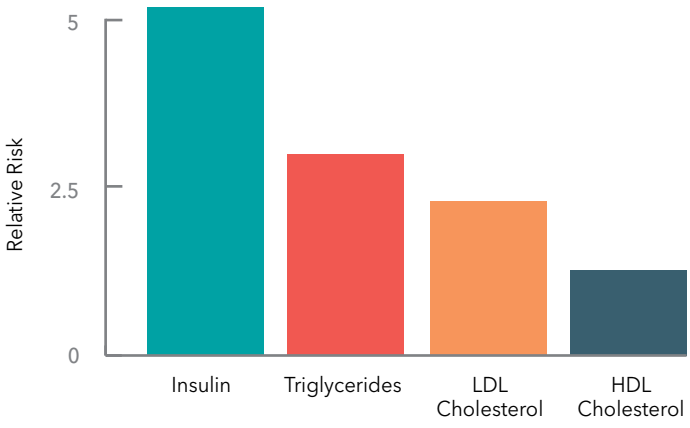


Figure 1

Cluster 1 was used as a control and was characterised by moderate diabetes progression risk accompanied by moderate insulin resistance and moderately abnormal TRGs and HDL levels.

Cluster 2 was characterised by low mortality together with a significantly lower risk of overt diabetes and coronary heart disease (CHD) than cluster 1. Insulin resistance was not a feature and TRGs and HDL were within normal limits.

Cluster 3 was characterised by high genetic risk (diabetes-associated G allele), the second highest progression to overt diabetes, pancreatic fat with disturbed insulin secretion, high carotid IMT but no increased CHD risk, however with a moderately elevated renal disease risk. Insulin resistance and TRGs were lower and HDL higher than in cluster 5.

Cluster 4 was characterised by predominantly subcutaneous fat ("healthy obesity") and low risk of progression to overt diabetes. This was accompanied by little insulin resistance, little liver fat, mild elevation of TRGs and mildly low levels of HDL.

Cluster 5 was associated with the highest progression to overt type 2 diabetes and all-cause mortality. It was characterised by high IMT, highest risk for kidney disease, highest insulin resistance, fatty liver, central obesity and the highest TRGs and lowest HDL levels.

Cluster 6 was characterised by high mortality in spite of low diabetes risk, most renal hilar fat and high risk for microalbuminuria and stage 3 renal disease, moderately high insulin resistance and TRGs level, moderately low HDL, high visceral fat and less liver fat.

At this stage of knowledge this study's clustering does not claim to be designed for definitive sub-phenotyping of patients. However, a few clinically useful conclusions may be drawn. In cluster 5 there is an imminent risk of established diabetes which should require intense diet and lifestyle intervention for weight loss and liver fat reduction. This applies also, albeit perhaps to a less intensive level, to cluster 3. In

cluster 6 insulin resistance, even with low glycaemia, appears to be responsible for renal disease and increased mortality. The pathogenesis of renal disease differs in type 1 and type 2 diabetes – glycaemia and hyperinsulinaemia respectively. This study also suggests fasting hyperinsulinaemia, TRGs and HDL levels are useful indicators of underlying early vascular pathology and the potential progression of prediabetes.

A recent study in *JAMA*[2] shows how the Mediterranean diet (mainly vegetables, legumes, fruit, nuts, seeds, olive oil, diary produce, fish and little red and preserved meat) lowers diabetes risk by 30% in overweight women. The most significant accompanying biomarker was a reduction of insulin resistance followed by HDL level improvement and BMI reduction, while LDL and HbA1c levels were irrelevant.

Fasting hyperinsulinaemia is an indication of chronically high insulin levels and insulin resistance. Chronic hyperinsulinaemia is associated with high blood pressure, increased platelet adhesiveness and atherosclerotic cardiovascular disease. Excess insulin (due to excess calorie consumption) accelerates ageing but not all calories stimulate insulin production to the same extent. Simple carbohydrates are the most powerful stimulators, protein to a much lesser extent, whereas fat has no effect on insulin.

The molecular basis of insulin resistance is unclear, but vascular endothelial dysfunction (a feature in type 2 diabetes) is the likely candidate, because insulin level in the interstitial space is lower than in the bloodstream. And endothelial dysfunction is the primary event in atherosclerosis.

A study published in *JAMA* in 1998[3] found that of the traditional risk factors for CHD, hyperinsulinaemia was more than twice as predictive as LDL (Figure 1). Also, TRGs were more predictive than LDL. One of the first signs of hyperinsulinaemia is increased TRGs. The fasting TRGs/HDL ratio is a surrogate marker for fasting insulin.

The pre-eminence of the predictive value of the TRGs/HDL for CHD risk was shown by a 1997 paper in *Circulation* (Figure 2).[4] Patients with the highest TRGs/HDL ratio were 16 times more likely to have a heart attack. High total cholesterol increased the risk by a factor of 2, while smoking increased the risk by a factor of 4.

Hyperinsulinaemia, and not fat (insulin neutral), would appear to be the main culprit in CHD. This crucial observation has been "hidden" from many cardiology departments by the huge LDL/statin industry (funding only statin/LDL trials). The finding that about 50% of patients hospitalised for CHD had total and LDL-cholesterol within normal limits[3] has also been overlooked. Statins probably improve CHD outcomes via their anti-inflammatory action on atherogenic lesions and not by lowering LDL.

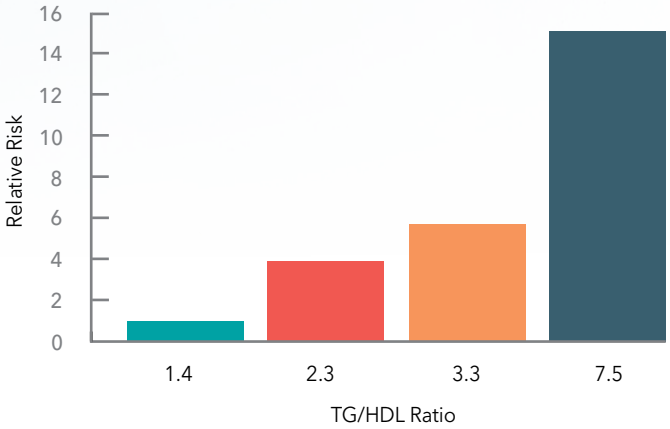


Figure 2

Reducing carbohydrate meal content (and alcohol) reduces insulin resistance, hyperinsulinaemia and the TRGs/HDL ratio. Marine omega-3 supplementation in adequate dosage (at least 3gm daily) also reduces TRGs.

Probably the most convenient method of assessing insulin production and diagnosing hyperinsulinaemia is measuring blood **C-peptide** level since this indicates how much insulin is being produced. Insulin and C-peptide are secreted into the portal vein in equimolar amounts but C-peptide's half-life is much longer than insulin's very short one and is therefore a more accurate measure of fasting/chronic insulin levels. Furthermore, the cumbersome OGTT test does not distinguish between insulin resistance and reduced insulin production. The C-peptide test seems simpler and superior to both blood insulin measurement and the OGTT. The C-peptide, HbA1c and TRGs/HDL ratio trio is suggested as a useful diagnostic and management tool in prediabetes and overt diabetes type 2.

To conclude, a very recent study[5] proposes another clinically useful prediabetes phenotypic cluster. In older adults (mean age 76 years), although prediabetes is common, the most common outcome is either return to normoglycaemia or death, and not progression to diabetes.

REFERENCES

1. Wagner, R., Heni, M., Tabák, A.G. *et al.* Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes. *Nat Med* 2021;27:49–57.
2. Ahmed S, Demler OV, Sun Q, et al. Association of the Mediterranean Diet With Onset of Diabetes in the Women's Health Study. *JAMA* Netw Open. 2020; 3(11); e2025466.
3. Lamarche B, Tchernof A, Mauriège P, et al. Fasting insulin and apolipoprotein B levels and low-density lipoprotein particle size as risk factors for ischemic heart disease. *JAMA* 1998; 279(24):1955-61.
4. Gaziano JM, Hennekens CH, O'Donnell CJ, et al. Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. *Circulation* 1997; 96(8):2520-5.
5. Rooney MR, Rawlings AM, Pankow JS, et al. Risk of Progression to Diabetes Among Older Adults With Prediabetes. *JAMA Intern Med.* Published online February 08, 2021. doi:10:1001/jamainternmed: 2020: 8774.

ENTRESTO® (sacubitril/valsartan) **Presentation**: Each film-coated tabletof Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex). **Indications**: In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. **Dosage & administration**:The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3-4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. **Contraindications**: Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy. **Warnings/Precautions**: Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. 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/valsartanis 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/valsartanimmediately 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 IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (ChildPugh 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. **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 co-administered 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/valsartanis 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. Interactions between sacubitril/valsartan and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of sacubitril/valsartan and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced 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 Cmax 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; Entresto49 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. 2020-MT-ENT-25-JUN-2020

References: 1. Seferovic PM, Ponikowski P, Anker SD, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of The Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2019;21(10):1169-1186. 2. Claggett B, Packer M, McMurray JJV, et al; for the PARADIGM-HF Investigators. Estimating the long-term treatment benefits of sacubitril-valsartan. *N Engl J Med.* 2015;373(23):2289-2290. 3. Lewis EF, Claggett BL, McMurray JJV, et al. Health-realted quality of life outcomes in PARADIGM-HF. *Circ Heart Fail.* 2017; 10(8):e003430. 4. ENTRESTO Summary of product characteristics. European Medicines Agency website. http://www.ema.europa.eu. Accessed 2020.

ENT AD1 12/20 MT

NOVARTIS

Entresto®
sacubitril/valsartan

PROF. ALEXIEI DINGLI

Ten Artificial Intelligence innovations

disrupting healthcare … close to home

The past year brought the world on its knees, yet it also ushered to the door several essential healthcare innovations. Telehealth and remote care became more widely available due to the restrictions imposed by the pandemic.

The strain on our health system meant that the most forward-looking medical institutions had to evolve new capabilities such as voice assistants capable of servicing hundreds of calls, over and above their usual complement. To speed up processing, Artificial Intelligence (AI) blossomed in various healthcare applications, with big data taking on a significant role in the field of predictive analytics.

These innovations are all rather impressive, and there are many more in the pipeline. However, most of them emerge from the top research centres located worldwide, such as the Mayo Clinic or some small start-ups tucked secretly in Silicon Valley. The truth is that many of them take a long time to become commercially viable, and it might be years before we start reaping their benefits. However, not all the innovation is happening on the other side of the world, and this article will highlight a few projects happening in our backyard. These are all currently being conducted by researchers at the University of Malta in collaboration with other entities such as Mater Dei Hospital. Their innovative aspect is at par with other projects happening abroad. The researchers do miracles with the meagre funds they receive, many of which stem from the University but also through national, European or even private funding. However, the thing they have in common is that very few people know about them, and for most of the time, the lack of subsequent financing kills the project. The following is a selection of such projects.

3D PRINTED SMART HAND

There have been various projects relating to the creation of artificial limbs. One of them uses the Open Hand Project to create a 3D printed hand and enhance it using smart components. The project's idea was to provide additional functionality to the artificial hand, such as changing the TV volume by moving the prosthetic arm from a distance. Voice recognition integrated within the hand allowed people to utter more complex commands sent back to any smart device in the house. Essentially, it fused a smartphone with an artificial limb.

MAPProHand PROJECT

The project seeks to build a commercial prosthetic hand from scratch. It aims to resolve the trade-off between simplicity, dexterity and usability typically experienced in commercial prosthetics. The project will conduct research on the hand's optimal dexterity based upon a simple architecture which guarantees its usability. It will then create an artificial hand based upon the parameters proposed by an AI system.

AUTISM VIRTUAL REALITY

The Autism Virtual Reality (VR) application, already discussed in a previous article, lets people experience what an autistic child goes through during a typical day. When the user wears the VR headset, he finds himself in a school setting where he sees, hears, and senses the world through an autistic child's eyes. The project aims to promote empathy, thus helping educators, careers and people interacting more thoroughly with autistic children.

CEREBRAL PALSY ASSISTANT

The SMARTCLAP project assists children with Cerebral palsy; the most common physical disability in children affecting movement and posture. The project places the user at the centre of the design process by creating a smart device which seeks to increase the child's motivation. During the various sessions, children sometimes find it challenging to perform the tasks which the therapist suggests. By changing the therapy into a fun game, the researchers hope to get better feedback from them. This concept is called gamification, whereby a typical (sometimes tedious) task, is changed into a game. Various experiments show that gamification is very useful in diverse settings. Through this project, the child is encouraged to develop positive behaviour and improve his social interactions.

AMBIENT ASSISTED LIVING

Ambient Assisted Living (AAL) services use technology in a person's daily life to help them live independently. Several AAL devices have been designed and developed, based on sensors, microphones and vision systems with quite promising results. However, for the field to reach maturity, many challenges need to be tackled, including developing robust processes in the real-world that are easy to use and accepted by society, users and carers. Because of this, researchers are trying to detect rare irregular events using just a standard camera system. Pose estimation models are used to detect a person in the image and extract the body keypoints. The

process is usually called skeletal detection, whereby the position of the person's skeleton is determined just from the picture. This information is essential to detect anomalies such as someone lying unconscious on the ground. Initial studies show some impressive results with the system capable of detecting most of the anomalies. These results also indicate that these methods compare very well with other commercial sensor-based solutions which are much more expensive and inaccessible for most people.

AUTOMATED GAIT ANALYSIS

Gait analysis is the systematic study of walking patterns which normally involves expensive and intrusive marker-based methods, in conjunction with multiple infrared cameras. When combined, they produce kinematic data that precisely measure the walking behaviour of a person. Once the data is collected, specialists then interpret the conclusions from the kinematic data to make diagnoses. On the other hand this project developed an automated alternative to marker-based methods for gait analysis using standard cameras and AI. The system achieves kinematic data that consists of varying left and right joint angles for hips or knees. Two video cameras pointed at the side and front view of a walking subject capture this information. It then uses pose estimation as a markerless form of motion capture which feeds into a pipeline of algorithms for calculating and processing kinematics. The automated method is quite promising since it achieves results almost identical to that of an expensive marker-based system. Thus it reduces the effort and financial investment needed for gait analysis, leading to a broader diffusion in the health care community. Furthermore, since such a system can theoretically work with just two mobile devices, it would make it ideal for use in remote areas worldwide where the availability of expensive setup is impossible.

SELF-HARM, DEPRESSION AND SUICIDE

The Mental Health Promotion (MEHAP) project tries to help adolescents with mental health issues, leading to self-harm, depression, and increased risk of suicide. The project will launch a mobile phone app co-produced with young people who have self-harmed themselves. It includes many features such as a mood monitoring diary, a personalised self-help menu of mood-lifting activities, audio-taped relaxation and mindfulness exercises. After every use, young people are asked to re-rate their mood and are routed to emergency numbers if they are still feeling an urge to self-harm.

SCHIZOPHRENIA VIRTUAL REALITY

A challenge with teaching health care workers about schizophrenia is that it is hard for them to understand what patients feel. This project uses AI in a VR simulation to immerse the users in a virtual world and help them experience the symptoms that such a patient might feel. The simulation features several simple tasks, which the user attempts while facing challenges associated with schizophrenia, in the form of visual and auditory hallucinations. AI is applied to the interactive narrative to allow the storyline to adapt to the user's actions, thus increasing the experience's immersiveness. Various mental health nursing students tried the experience, and it was well-received. It managed to increase their awareness and fostered empathy for people having schizophrenia. The next phase in this project is to use it as a treatment for the actual patients whereby patients can confront their hallucinations in a safe virtual setting.

PAIN REDUCTION

If the brain is distracted, the perception of pain is decreased even though the stimulus is still present. The idea of distraction as a pain management technique is not novel, and there are several case studies where this was proven to reduce pain perception by up to 50%. VR headsets distract children during routine painful procedures and treatments.

In the UoM's Morpheus project, the researchers are using biosensors like smartwatches to read biological information. This data will make the VR experience change and adapt in real-time, in relation to what the patient is feeling. If a patient is bored, the game will become exciting. If he is anxious, it slows down and becomes more calming. The initial results have shown that the VR experience is much more effective and reduces the pain felt without the need to resort to any medication.

CANCER DETECTION

Another project which was due to start a few years back uses AI to detect abnormalities in radiographs. The idea was to analyse the imaging data and point radiologists at potential abnormalities. This project would speed up their work drastically and increase their accuracy since some cancers can be easily missed even with the trained eye. In keeping with this, an article published in *Nature* in 2020, on the application of AI in breast cancer screening, reported a reduction in both false positives and false negatives, when compared to standard radiologist screening.[1] This result does not mean that an AI will replace a doctor any time soon. However, it is an opportunity for any doctor to get a second opinion of his diagnostics in no time and at a meagre cost, thus further reducing the human error rate. This project was the brainchild of Professor Aaron Casha, a brilliant surgeon and visionary who sadly died last year. Unfortunately, the project died with him too.

CONCLUSION

As one can see, the ongoing projects are various, and they touch with all areas of health. Probably there are many other projects which we are not listing here! This list was just a selection to celebrate the researchers involves and to showcase their novelty. These researchers go to great lengths to secure funding, find partners, work on the project, and keep it going after the funds dry out. However, the medical and tech worlds are still far apart. So when an idea brews, take the first step, reach out to the various researchers, and turn it into reality. After all, these innovations are essential to make the lives of people better.

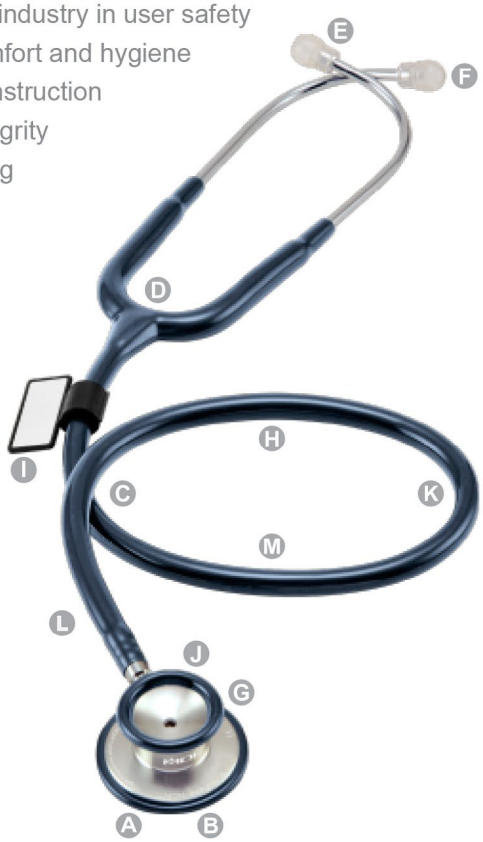
REFERENCE

1. McKinney SM, Sieniek M, Godbole V et al. International evaluation of an AI system for breast cancer screening. *Nature* 2020; 577:89–94.

Y0821

MDF instruments®

- **A** **Handcrafted** in the MDF® artisan tradition by master craftsmen since 1971
- **B** **Ultrasensitive diaphragm** delivers superior high-frequency amplification
- **C** **REACH >** European Community Regulation on Health and Environment
- **D** **Patented ErgonoMax™** headset is anatomically angled for a precise fit
- **E** **Patented SafetyLock™** eartip adaptors lead the industry in user safety
- **F** **Soft silicone ComfortSeal™** eartips provide comfort and hygiene
- **G** **Super-duty** lightweight aluminum chestpiece construction
- **H** **Insulated** acoustic tubing optimizes acoustic integrity
- **I** **Included accessories:** eartips, diaphragm, ID tag
- **J** **Large bell** is crowned with a non-chill ring
- **K** **Free-Parts-for-Life Program**
- **L** **Lifetime warranty**
- **M** **Latex free**



JAMESCO
TRADING COMPANY LIMITED
Tel: 21314333

- Cosmo™ MDF1
- BluBabe™ MDF3
- Abyss™ MDF4
- Cher MDF7
- Purple Rain MDF8
- OM™ MDF9
- Maliblu™ MDF10
- NoirNoir™ MDF11
- S.Swell™ MDF14
- Napa™ MDF17
- RedEnv™ MDF23
- BlackOut™ MDFBO

Acoustica™ STETHOSCOPE

The MDF® Acoustica™ Stethoscope is a lightweight diagnostic instrument that delivers accurate auscultation of heart, lung, and Korotkoff sounds with acoustic integrity and clarity. Precisely handcrafted, the Acoustica™ is the ultimate in auditory diagnostics with unmatched performance and durability.

CRAFTING WELLNESS

SINCE 1971

DR PIERRE VASSALLO

Imaging Tumours of the Ovary
Part 1

The ovary is the site of several different tumours because it contains many different cell types and due to its proximity to the fallopian tube.[1] While most ovarian tumours are benign or borderline, ovarian cancer is the second most common gynaecologic malignancy and the fifth most common cause of death in women.[2]

The ovary is composed of a connective tissue stroma, which in premenopausal women, contains ovarian germ cells called oocytes. Oocytes vary in number based on the patient's age. They are surrounded by a layer of granulosa cells and an outer layer of thecal cells. The surface of the ovary is lined by a special layer of epithelium known as ovarian surface epithelium; the proximal (fimbrial) end of the fallopian tube lies close to the ovarian surface epithelium.[3]

Despite having ligamentous attachments to the uterus, fallopian tube and pelvic wall, the ovary is mobile within the peritoneal cavity. These ligaments act as passageways for the spread of cancer.

Ovarian tumours can be broadly divided into four main groups: epithelial cell, germ cell, sex cord stromal and metastases.

Epithelial tumours are the most common group of ovarian tumours with benign serous cystadenoma being the most common tumour overall accounting for 30% of all ovarian neoplasms. On the other hand, high grade serous adenocarcinomas (HGSCs) are the most common subtype of malignant ovarian tumours, most commonly seen in women over 61 years of age and constituting the most common cause of death from ovarian cancer.

While a histologic diagnosis that is based on tissue biopsy is required for further management, diagnostic imaging provides important information on the most likely tumour type as well as tumour size and spread. This data is needed to guide pre-operative management including surgical planning and to monitor the impact of treatment.

HISTOLOGIC SUBTYPES OF OVARIAN TUMOURS

Ovarian epithelial tumours do not contain cells that resemble any of those normally present in the ovary. Thus, ovarian epithelial tumours are not truly primary. There is considerable evidence that shows that serous epithelial cells slough off from the fimbriated end of the fallopian tube and enter the ovary through the site of rupture of its surface that occurs during ovulation; this collection of fimbrial epithelial cells inside the ovary is called an epithelial inclusion cyst.[4] In keeping with the above, there is strong evidence that HGSCs arise from sloughing off of malignant cells from the fimbriated end of the fallopian tube.[5]

The origin of mucinous epithelial tumours is less well understood, but recent studies have suggested that they may originate from pluripotential cells present in ovarian teratomas or Brenner tumours.[6]

Endometroid and clear cell epithelial tumours appear to arise from retrograde menstruation within endometrial implants or endometriomas.

Germ cell and sex cord stromal tumours are true primary ovarian tumours that originate from primitive germ cells, sex cord and stromal cells of the ovary.

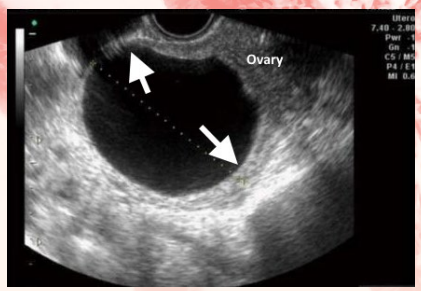


Figure 1. Transvaginal US image shows claws of normal ovarian tissue (arrows) surrounding a small ovarian tumour (serous cystadenoma).

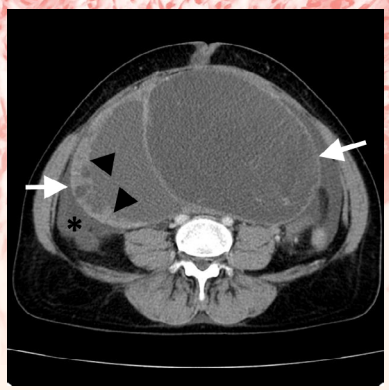


Figure 2. CT Scan showing a low grade serous carcinoma (LGSC) (white arrows) with thick cyst walls (arrowheads) and ascites (*).

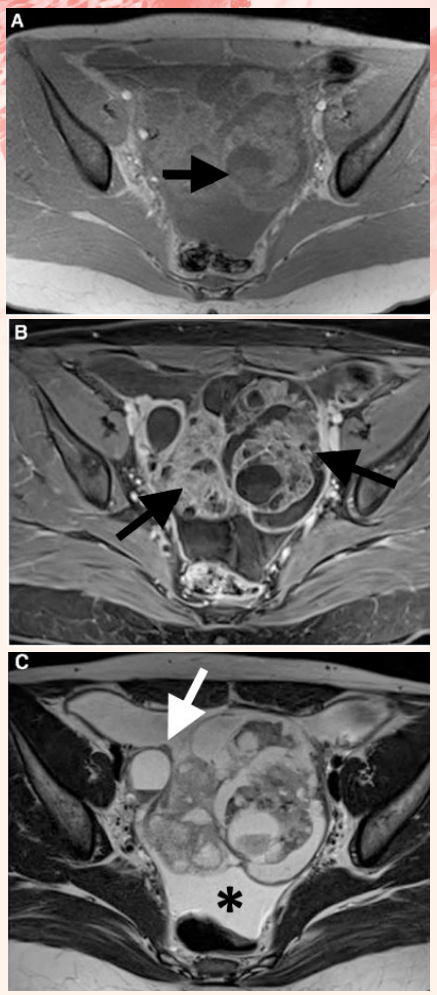


Figure 3. T1 weighted fat saturated pre- (A) and post-contrast (B) MRI images show a complex pelvic mass with solid components (arrows) that shows strong contrast enhancement (B). The T2 weighted image (C) depicts ascites (*) and peritoneal metastases (white arrow).

Metastases reach the ovary from other organs through haematogenous, lymphatic, or direct spread; they originate mostly from the gastrointestinal tract, breast, lungs, and contralateral ovaries.

CLINICAL FINDINGS, RISK FACTORS AND TREATMENT

Smaller benign ovarian tumours are often discovered incidentally during routine imaging studies. Larger malignant and mostly epithelial type tumours present with bloating, pelvic/abdominal pain, satiety and urinary urgency and frequency. Epithelial tumours are more common in older women, while germ cell tumours are more often seen in younger women.

Risk factors for epithelial tumours include older age, obesity, a history of colorectal cancers, and familial cancer syndromes (BRCA1, BRCA2, Lynch syndrome and Peutz-Jeghers syndrome) and fertility treatments. Smoking is a risk factor associated with mucinous tumours. A genetic predisposition is seen in up to 25% of ovarian cancers.

Since the risk for ovarian cancers is high in those with genetic predisposition, screening with transvaginal US and cancer antigen 125 (CA-125) as well as prophylactic salpingo-oophorectomy have been advocated.[7]

Treatment is based on tumour stage (International Federation of Gynaecology and Obstetrics – FIGO system). Large tumours are surgically debulked and then treated with adjuvant chemotherapy. Neo-adjuvant chemotherapy may be used with extensive disease to induce reduction in tumour size prior to surgery. Monitoring of CA-125 levels allows disease surveillance with most types of tumour.

IMAGING OVARIAN TUMOURS

US, MRI and CT are all useful and offer complementary information for detecting ovarian tumours and assessing their extent; it is normal to employ at least two of these modalities (usually US and MRI) in pre-operative management with CT being used for post-operative follow-up.

Transvaginal US is particularly useful as the first imaging modality and for assessment of smaller ovarian tumours, while MRI allows further tumour characterisation and visualisation of the extent of larger tumours. Transabdominal US allows preliminary assessment of the extent of large tumours, but MRI is the imaging modality of choice for large lesions.[1] Colour and greyscale Doppler US is useful for assessing

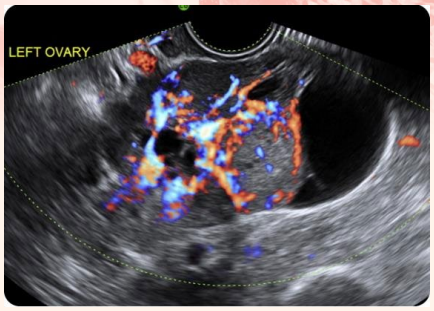


Figure 4. Transvaginal US of an LGSC appearing as complex ovarian tumour with abundant colour flow on Doppler imaging.

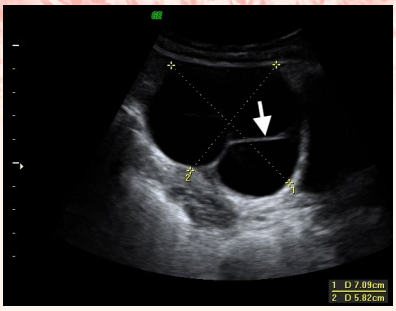


Figure 5. Transvaginal US showing a serous cystadenoma presenting as a unilocular cyst with thin walls; no mural nodules or papillary projections are evident. This tumour type may also present with multiple cysts; however these should exhibit thin walls (arrow) with no mural nodules, papillary projections, or septal vascularity.

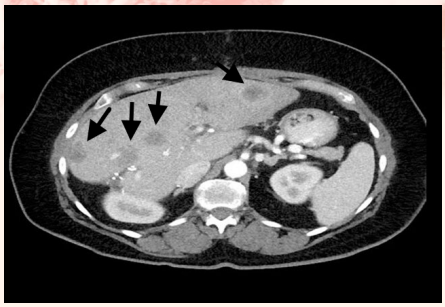


Figure 6: CT scan showing HGSC metastases in the liver (arrows).

tumour vascularity and ovarian torsion that may occur secondarily with an ovarian mass.

Ovarian imaging should confirm the ovary as the organ of origin of the tumour and whether the tumour is most likely benign, borderline, or malignant.

Smaller tumours may show a rim or claw of normal ovarian tissue around them, which will confirm that they are of ovarian origin (Fig 1). With larger tumours, the ovary itself may not be visible; its ovarian origin can only be established through its proximity to the bladder, uterus and bowel (Fig 2). An ovarian vein seen entering the tumour on CT or MRI scans also helps to identify its ovarian origin.

MRI allows better soft tissue characterisation; it also helps confirm suspected ovarian torsion. CT is useful as a rapid and accurate test for detecting fat and calcification within the tumour and for monitoring the impact of therapy in reducing tumour size. CT is also useful for detecting complications such as bowel obstruction and rupture.[1]

US findings that point towards a malignant ovarian tumour include large tumour size, multilocular lesions, papillary projections, irregular inner wall or irregular septa, solid tumour components (Fig 3) and blood flow with the lesion (Fig 4). Patients with lesions that demonstrate these features should be referred for gynaecological consultation.

Indeterminate lesions, such as complex lesions or those whose origin cannot be identified with certainty, should be further assessed with MRI. The presence of fat, haemorrhage or fibrous components within an ovarian tumour can be detected with MRI.

For staging of ovarian cancer, CT is the examination of choice since bowel motion and respiratory artifacts tend to limit the usefulness of MRI particularly for detecting peritoneal metastases. Peritoneal metastases measuring less than 5mm in diameter are not visible on CT particularly when they lie on the bowel surface or on the mesentery. CT is particularly useful for pre-operative staging, for restaging after debulking surgery and to detect complications such as intestinal obstruction.[8]

Epithelial Tumours

Epithelial tumours are classified as benign, borderline, or malignant based on histologic features that include extent of epithelial cell proliferation, degree of nuclear atypia and the presence or otherwise of stromal invasion.

Benign epithelial tumours typically present as unilocular cysts lined by a single layer of epithelium (Fig 5). Borderline tumours do not show evidence of invasion but may exhibit peritoneal spread. Malignant epithelial tumours may be low or high grade; low grade tumours are thought to arise from borderline lesions, with low grade malignant tumours showing stroma invasion.

Serous epithelial tumours are the most common ovarian neoplasms followed by mucinous epithelial tumours. Benignand borderline serous epithelial tumours, and low grade serous adenocarinomas are considered different entities from high grade serous cystadenocarcinomas. While mucinous cystadenoma, borderline, and mucinous adenocarcinomas are considered to be a continuum of the same tumour class.

The distinguishing feature between epithelial inclusion cysts and unilocular serous cystadenomas

is size, where the latter measures >1cm in diameter. In patients who are still ovulating, a unilocular cystic lesion measuring >1cm in diameter is indistinguishable from an ovulating follicle. In this situation, a repeat endovaginal pelvic US after 6 weeks should be performed. Persistence of unilocular cyst on follow-up imaging would distinguish a serous cystadenoma from a functional ovarian cyst (follicle).

Serous epithelial tumours are commonly bilateral, while mucinous tumours are mostly unilateral. Borderline and malignant serous tumours may show early peritoneal spread, while mucinous borderline and malignant tumours tend to remain confined to the ovary unless they rupture, which can lead to pseudomyxoma peritonei.

Imaging features of epithelial tumours that point towards a borderline or malignant tumour include mural nodules, papillary projections, enhancing non-fatty and non-fibrous solid components, septa that are 3mm or more in thickness and septal vascularity. Large lesions and the presence of peritoneal or nodal spread are also indicative of a borderline or malignant lesion. Distant organ metastases are more commonly seen with HGSCs (Fig 6).

CONCLUSION

The above article introduced important clinical and imaging facts relating to ovarian tumours and discussed mainly serous epithelial tumours, the most common histologic subtypes. Part 2 of this article will present mucinous epithelial, germ cell, and sex cord stromal tumours as well as metastases.

REFERENCES

1. Taylor EC, Irshaid L, Mathur M. Multimodality Imaging Approach to Ovarian Neoplasms with Pathologic Correlation. Radiographics 2021;41(1):289-315.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66(1):7-30.
3. Chhieng D, Hui P, eds. Cytology and Surgical Pathology of Gynecologic Neoplasms. New York: Spinger; 2011. .
4. Klotz DM, Wimberger P. Cells of origin of ovarian cancer: ovarian surface epithelium or fallopian tube? *Arch Gynecol Obstet* 2017;296:1055–1062.
5. Labidi-Galy SI, Papp E, Hallberg D, et al. High grade serous ovarian carcinomas originate in the fallopian tube. Nat Commun 2017;8(1):1093.
6. Ricci F, Affatato R, Carrassa L, et al. Recent Insights into Mucinous Ovarian Carcinoma. *Int J Mol Sci* 2018;*19*: 1569.
7. Rosenthal AN, Fraser L, Manchanda R, et al. Results of annual screening in phase I of the United Kingdom familial ovarian cancer screening study highlight the need for strict adherence to screening schedule. *J Clin Oncol* 2013;31(1):49-57.
8. Jeong YY, Outwater EK, Kang HK. Imaging Evaluation of Ovarian Masses. Radiographics 2000; 20(5): 1445-1470

Energast

150 mg of sodium butyrate

Proven efficacy in intestinal diseases

Energast benefits for the patients demonstrated in observational trials with following cases:

- Irritable bowel syndrome (IBS)
- Ulcerative colitis
- Crohn's disease
- Diverticular disease
- Intestinal flora disorders
- Intestinal inflammation following radiotherapy and chemotherapy
- Intestinal infections
- Diarrhoea of different etiology

FOR HEALTHY INTESTINES CLINICALLY PROVEN

Microencapsulated sodium butyrate

For more information contact Rachel Grech on **Tel: (+356) 9942 9974**
or Email: **rachel.grech@pac3.eu**

PAC3