

FATTY LIVER DISEASE AND THE CONSEQUENCES FOR EUROPE



Health in Europe: A matter of good economics

Adjacent Government details the priorities and intentions of the new European Health Commissioner, Vytenis Andriukaitis...



Born in 1951, Vytenis Andriukaitis holds degrees in medicine and history and started his political career just after high school. He is one of the authors of the Lithuanian Constitution of 1992 and a signatory to the 1990 Act of the Re-Establishment of the State of Lithuania. Andriukaitis entered politics in 1976 as an underground Social Democrat, and was among those who re-established the Social Democratic Party of Lithuania in 1989. He was an active member of the Lithuanian Reform Movement *Sąjūdis*, fighting against the Soviet, before becoming an active politician. He has also served as a cardiovascular surgeon for almost 20 years.

Andriukaitis was also the Minister of Health in the Republic of Lithuania from 2012-2014, and is currently the Vice-President of 67th World Health Assembly.

MEPs approved the new college of 27 Commissioners, including Andriukaitis, as presented by its President-elect Jean-Claude Juncker in October 2014, and is a welcome appointment according to The European Public Health Alliance. Andriukaitis spoke at their

annual conference in 2014 where he said, "Health is not a consequence of growth but also a condition for growth. Investments in public health increase productivity and boost job creation. Health should not only be seen as product of growth: health encourages growth."

Emma Woodford, EPHA Interim Secretary General reacted to his appointment stating that, "Better attention should be paid to socio-economic determinants of health, health promotion and prevention. Once he is confirmed as Health and Food Safety Commissioner by the European Parliament in October, he should put forward an agenda based on greater investments in health with a focus on social determinants."

Andriukaitis has long held the belief that health policy has a key role to play in economic growth, repeating again the sentiment that "healthy people are more creative and productive. Their well-being sets the foundations that moves societies forward. Health in all policies should be the driving force of our efforts to cut inequalities as it lays the groundwork for social justice and economic sustainability".

for healthcare, he will support efforts to make health systems more efficient and innovative; so that they can provide equitable healthcare to all citizens, while remaining financially sustainable;

- To assess the performance of health systems reform within the European Semester;
- To focus on enhancing prevention, as the more health systems invest in this field, the less they will pay for treatment in the future;
- Andriukaitis will seek to make recent EU legislation having an impact on the protection of public health deliver results to citizens. For example, to ensure the timely adoption of secondary legislation foreseen under the Tobacco Products Directive. He intends to work tirelessly with the Member States to ensure the Directive on patients' rights in cross border healthcare translates into citizens' better access to quality care; into in-depth co-operation on e-Health towards better care; and into joint work on Health Technology Assessment to improve patients' access to innovative technologies, business predictability and cost-effectiveness;
- Working with Member States to protect citizens against any cross border health threat;
- Promoting healthy and safe food as a means to prevent unnecessary spending in healthcare and help Member States improve the long term sustainability of their health systems;
- Endeavour to ensure high levels of animal and plant health, providing strict controls on the safety of imported products of both plant and animal origin;
- To work with all stakeholders to maintain and improve food safety systems contributing to President Juncker's plans for a Europe with more jobs and greater prosperity, particularly for SMEs which make up the bulk of the food sector.

Andriukaitis made it clear that all legislative proposals currently under discussion with the European Parliament and the Council are brought to a successful

In his written answers to questions from MEPs before his official appointment, he provided details of what his top priorities would be in the fields of public health and food safety:

- With regard to past crises such as BSE and SARS, which have shown the economic value of strong health protection, he intends to pursue the highest standards;
- He believes we need 'a new boost for health in Europe' if we are to improve people's health and boost jobs and growth. He therefore intends to "promote investment in health, as an investment in Europe's human capital and an investment in our future";
- The priorities surround promotion, protection and prevention. Andriukaitis intends to deliver real benefits to citizens and support key sectors of the EU economy such as the healthcare sector – as well as the agro-food industry;
- Against a backdrop of population ageing, a growing burden of chronic diseases and increasing demand



conclusion, including the proposals on animal health, plant health, official controls, novel food, cloning, zootechnics and medicated feed. He also promised that within the first 6 months he would review the legislation applicable to the authorisation of genetically modified organisms.

Health systems performance assessment

In his speech on the 27th January at the launch of the European Health Consumer Index 2014, Andriukaitis reiterated his priority as mentioned above. Namely – promotion, prevention, protection, but also added ‘participation’ in thanks to his young followers on social media. He also referred to the importance of health systems performance assessment – a useful tool to understand how we work and how we can improve. He believes that the assessment will build up knowledge which can help make evidence-based policies at national and European levels. Member

States and the Commission have agreed to pursue a set of common goals, the first of which is a forum where they could:

- Exchange their experiences;
- Present their practices;
- Share success stories; and
- Learn from each other.

The second goal is to support national policy makers by identifying tools and methodologies to improve the assessment of their health systems. Cooperation will also take place with organisations such as the OECD and WHO.

Health information

According to Andriukaitis “health information is at the foundation of good performance assessment”, with



the European Commission making considerable efforts to “reinforce and ensure the sustainability of actions on health information”. Data collection supported by the Health Programmes has led to:

- Improvements of the methodology of statistics collection;
- Development and harmonisation of health indicators; and
- The preparation of health reports.

Andriukaitis recognises that these steps don’t go far enough in themselves and wishes to ensure:

- The sustainability of data collection;
- Transparency in the development of indicators; and
- Full participation of Member States in their selection.

For Andriukaitis to realise the intentions and priorities he has laid out, he will need all the enthusiasm and stamina he can muster. An immediate topic at the forefront is the potential for a US free-trade deal agreement which could equate to the world’s biggest trade deal to date. However, with no clear majority emerging as yet, and with public opposition within Europe apparent, Andriukaitis will have to work hard to ensure buy-in by all national parliaments. No doubt the negotiations needed to ratify this deal would provide him with an early legacy, but there is still much to do, not just with the free-trade agreement, but on his promises made last year.

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Fatty Liver Disease and the future consequences for Europe

Alterations in our lifestyle over the last decades, including high caloric intake (e.g. through high fructose and high fat diet) combined with a sedentary lifestyle have augmented the worldwide incidence of overweight and metabolic syndrome, characterised by abdominal obesity, insulin resistance and Type-2 diabetes, hypertonia and dyslipidemia. This trend is not only observed in industrialised countries in the US or Europe but also gradually now in developed as well as developing countries. At the moment it is believed that approximately 90 million Americans and 40 million Europeans suffer from a fatty liver (also called Non-alcoholic fatty liver disease (NAFLD)).

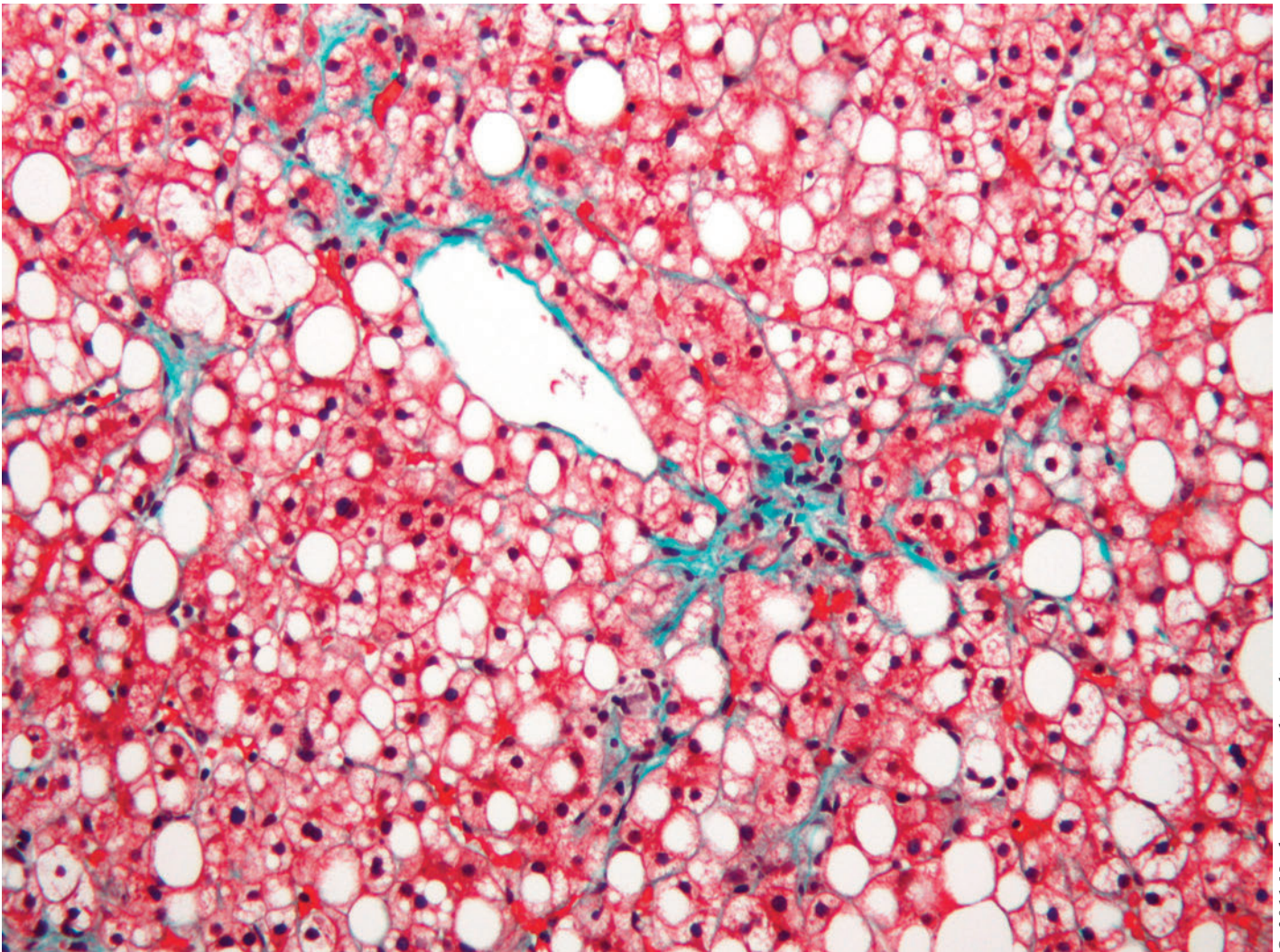
Consequently, the price we will have to pay – from a global point of view – for our consequent aim to achieve progressive industrialisation and enhanced economic development in the 3rd world as well as developing countries is the adaptation to the 'Western' unhealthy diet and its concomitant lifestyle. It should also be mentioned that particularly this development – in the long run – will lead to a huge problem as developing and developed countries will contribute greatly to the number of people suffering from the metabolic syndrome and fatty liver disease. It is estimated that more than 100 million people will suffer from fatty liver disease, the metabolic syndrome and its consequences from China and India alone. From a European point of view, a further increase of the metabolic syndrome as well as fatty liver disease is to be expected – underlining the need of therapeutic options to efficiently treat these patients in the next 20 years.

We know today that overweight and metabolic syndrome lead to diseases of several kinds, including coronary heart diseases, Type-2 diabetes but also cancer (e.g. liver cancer, colorectal cancer). Epidemiological data clearly indicate that overweight and metabolic syndrome are reaching pandemic dimensions in industrialised countries – and can be

seen to a high degree in the US and in Europe. As mentioned above, it is prospecting that newly developing countries – as a consequence of industrialisation and adaptation of their lifestyle – will also experience a steep increase in overweight and metabolic syndrome-triggered diseases. In the past 10 years, the rate of obesity has doubled in adults and tripled in children in the US. A similar trend has also been observed in Europe, and this trend will accelerate and steepen.

The liver – which is the most important metabolic organ – is strongly affected by a chronic state of overweight and metabolic syndrome. Non-alcoholic fatty liver disease (NAFLD), which is the most frequent liver disease worldwide, is a clinical manifestation of overweight and metabolic syndrome. NAFLD is a chronic disease that can last several decades, characterised by predominant macrovesicular steatosis of the liver and that can easily become more. Although the prevalence of NAFLD is increasing globally, epidemiology and demographic characteristics of NAFLD vary worldwide. It is becoming increasingly clear that a number of pathways are involved in the pathogenesis of NASH, and its progression to advanced stages of liver disease. These pathways may be diverse in different cohorts of patients with NASH. Understanding of which pathways play a role in the development of NASH will be critical before launching treatment modalities.

A significant number of NAFLD patients develop non-alcoholic steatohepatitis (NASH), fibrosis and consequently hepatocellular carcinoma (HCC). In recent years, obesity leading to metabolic syndrome, steatosis and steatohepatitis has attracted increased attention due to an increased HCC incidence in the US and Europe. In line, the most common etiology for HCC in industrialised countries has recently switched from chronic viral infections (e.g. Hepatitis B and Hepatitis C virus) to obesity, making HCC the most



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Micrograph of non-alcoholic fatty liver disease (NAFLD). Masson's trichrome & Verhoeff stain. The liver has a prominent (centrilobular) macrovesicular steatosis (white/clear round/oval spaces) and mild fibrosis (green). The hepatocytes stain red. Macrovesicular steatosis is lipid accumulation that is so large it distorts the cell's nucleus. Differential diagnosis of centrilobular (zone III) macrovesicular hepatic steatosis: Diabetes. Obesity. Alcohol.

rapidly increasing type of cancer in the US, with a similar trend observed in Europe. Today, we lack a detailed understanding how chronic steatosis develops into NASH and what factors control its transition from NASH to HCC. At the same time no therapeutics exist to efficiently treat NASH, and treatment options for the therapy of late stage HCC are limited and only prolong the life span of patients between 3 to 6 months.

In laboratory mice, NASH can be induced by several different diets such as methionine/choline-deficient diet (MCD) or choline-deficient diet (CD) but not by high fat diet (HFD) alone. However, C57BL/6 mice fed with MCD or CD do not develop obesity or metabolic syndrome and the diet has to be discontinued after a few months due to weight loss (up to 40%) or occasional cachexia. Thus, these approaches do not recapitulate

NASH and its consequences (e.g. transition to HCC) in humans and appropriate mouse models for genetically and mechanistically dissecting NAFLD induced NASH and NASH triggered HCC development have been thus far lacking.

Deficiency in the essential nutrient choline was described in NAFLD patients to exacerbate NAFLD and NASH. Moreover, humans with inadequate choline uptake were shown to have defects in hepatic lipoprotein secretion, oxidative damage caused by mitochondrial dysfunction and ER stress.

Based on the clinical observations of choline deficiency to exacerbate NAFLD and NASH patients, we have recently combined choline deficiency with a high fat diet (CD-HFD) as a chronic diet for laboratory mice, which may lead to metabolic syndrome,

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steatosis, liver damage and NASH, thus delivering the ‘second hit’ that promotes dietary-induced liver carcinogenesis – similar to the human situation. This approach enabled us to establish a chronic mouse model of NASH and metabolic syndrome, triggering subsequent HCC in a wild-type C57BL/6 mouse, in the absence of chemical carcinogens or genetic mutations predisposing to NASH or HCC development (Wolf et al., Cancer Cell, 2014). CD-HFD treated mice display obesity, overweight, insulin resistance, liver damage and fibrosis and hepatic mitochondrial damage, dyslipidemia and NASH as observed in human patients. HCC developed 12 months post CD-HFD start and resembled histologically, genetically and morphologically human HCC. Interestingly, by using this novel model we could investigate the cellular and molecular mechanisms that drive NASH and NASH to HCC transition. Results of our work show that adaptive immune cells (e.g. cytotoxic T-cells as well as Natural Killer T cells) greatly contribute to the diet induced liver pathology and affect the degree of liver damage as well as the degree of lipid uptake in hepatocytes, thus priming the liver to develop from a fatty liver to a liver with NASH pathology. Moreover,

we could show that some of those immune cells expressed and secreted several inflammatory cytokines that appeared to be the underlying effector molecules to drive pathology. The most prominent candidate of all cytokines tested was a tumor necrosis factor super family member called LIGHT, which stands for “homologous to Lymphotoxins, Inducible expression, competes with HSV Glycoprotein D for HVEM, a receptor expressed on T-lymphocytes”. Genetic ablation of this cytokine sufficed to prevent NASH as well as NASH to HCC transition. Thus, this cytokine would potentially represent a therapeutic target for pharmacological interventions.

Consequently, we took the next step and asked whether our NASH mouse model would indeed reflect human pathology. Thus, we also analysed NASH patients and patients suffering from other liver diseases with concomitant lipid deposition (e.g. Chronic HCV infection, alcoholic steatohepatitis) and could find comparable activated immune cells in livers of NASH patients. Moreover, we found similar cytokines expressed in the livers of NASH patients as we had found in our mouse model to be causally



linked to NASH and HCC disease development. Remarkably, upregulation of LIGHT, a cytokine that belongs to the TNF superfamily, was highly characteristic for NASH when compared to other diseases that contain increased lipid deposition (see above).

We thus believe that our mouse model recapitulates several pathophysiological aspects of human NASH and provides a mouse model enabling to study the development of NASH and NASH to HCC transition. In the future the link between activated T-cells in the liver and their crosstalk to hepatocytes could give us important insights in how we can generate novel therapeutics for treating NASH as well as NASH induced HCC in industrialised countries. The foreseeable development of NASH into a pandemic disease in Europe will force health authorities to act. To some extent first measures have been taken but the wave of cases that is expected to come will not be prevented with the current political initiatives as well as with the current attempts to support education and research. It will need strong political efforts to change the thinking of our idea about living, about nutrition as well as about preventive measures each

individual person can take to lead a more healthy life. Moreover, research has to be strongly supported to find – besides a European wide political strategy of prevention – therapeutic measures to prevent, to early diagnose and to treat NASH as well as subsequent diseases of NASH. The monetary effort for such political, educational as well as research programs will surely be just a small proportion to what will be needed in 20 years from now to treat people with established metabolic syndrome and subsequent diseases such as NASH, cardiovascular problems and liver cancer. From my point of view the clock is ticking and unfortunately it appears as if European political decision makers rather want to wait to become active until this problem is evident. This of course is the worst case scenario but it would not be the first time that only if a severe problem is present measures will be taken. This is what clinicians would call therapeutic approach. I propose a preventive and therapeutic approach: Support research and find novel drugs to treat the present disease but combine it with preventive measures (e.g. workout) in those individuals who are at high risk to develop metabolic syndrome, NASH and liver cancer.

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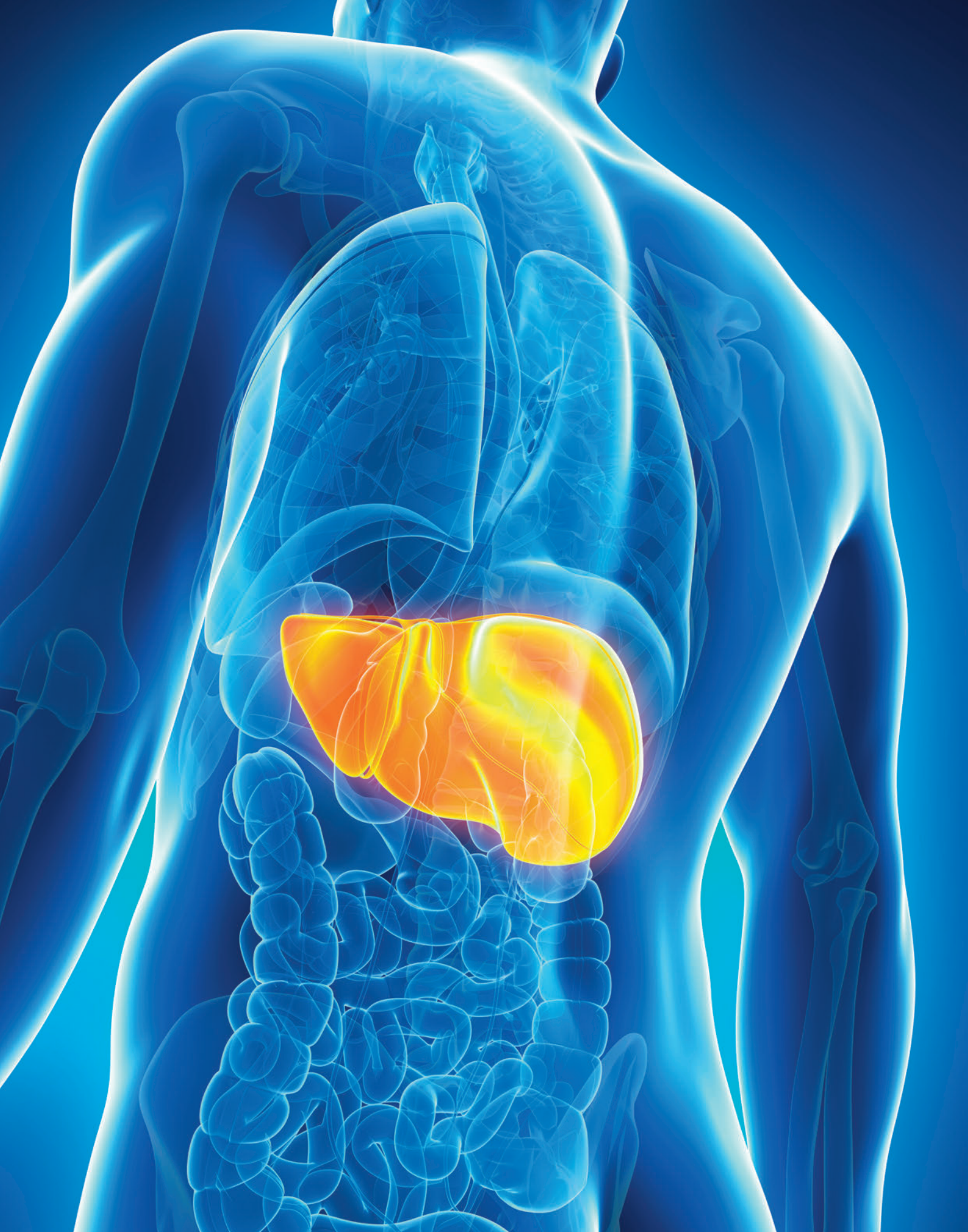
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