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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".

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 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 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.

"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 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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Introduction

Physicians have long been aware of the subtle differences between patients and their responses to medications. The recognition that a part of this variation is inherited, and therefore predictable, created the field of pharmacogenetics several years ago.

Pharmacogenetics studies the influence of genetic variation on drug response. Genetic variation is considered an important source of variability in drug response and contributes to 25% - 50% of inappropriate drug responses.[1] It has the potential to negatively impact effectiveness of drug therapy ('drug efficacy') and increases the risk for dangerous side effects, termed adverse drug reactions (ADRs). Linking the genetic source of variability to drug response is often clinically significant and meaningful.[2, 3]

A patient's response to a drug is often linked to common genetic variations present in their genes. One type of genetic variation is the single nucleotide polymorphisms (SNPs). Knowing the types of SNPs genetic variations present in a patient can help predict the associated drug response. This can not only help physicians individualize drug therapy, it will also help improve effectiveness of the drug, decrease the chance of adverse drug reactions and reduce healthcare costs.[4]

Pharmacogenetics 101

(Reference: http://www.genome.gov)

- Single Nucleotide Polymorphism (SNP)—Genetic variation arising from substitution of one base pair in DNA for another base pair is referred to as a SNP. SNP is a genetic mutation in the DNA that can result in a disease phenotype.
- Haplotype—Combinations of several SNPs together on the same chromosome.
- Alleles—Alternative forms of a gene that arise by mutations in the DNA.
- Genotype—An individual's collection of genes. The term also can refer to the two alleles inherited for a particular gene. The genotype is expressed when the information encoded in the gene is used to make protein.
- Phenotype—The expression of the genotype contributes to the individual's observable traits.

Accurate prediction about drug response is crucial for individualized treatment. This is best made by combining an individual's genetic data with clinical findings and classifying patients into subpopulations based on their response to a specific drug.[5] Using this approach, health care providers can move beyond the "one-size-fits-all" strategy and identify treatments that are more personalized.

The discovery of genetic factors such as the cytochrome P450 (CYP) drug metabolizing genes and several years of subsequent clinical research have added to the understanding of the clinically relevant genetic variations that may help predict drug response.

Genetic Variation and Drug Efficacy

The extent to which patients metabolize drugs has a significant impact on the effectiveness of their therapeutic effect.

Genetic variation in CYP450 metabolizing genes plays a major role in variability in drug response.[7] To a large extent the CYP450 genotype of a patient determines the level of enzyme activity ('phenotype') which can be classified into four groups:

- **Extensive metabolizers (EMs)** have normal enzymatic activity, and carry either two wild-type alleles, or one wild-type allele and one decreased activity or null allele.

- **Intermediate metabolizers (IMs)** have decreased enzymatic activity, and carry either two decreased activity alleles, or one decreased activity allele and one null allele.
- **Poor metabolizers (PMs)** have absent enzymatic activity, and carry two null alleles.
- **Ultra-rapid metabolizers (UMs)** have increased enzyme activity, and have gene duplications or multiplications of the CYP2D6 gene (more than two copies of the gene)[8]

Typical drug efficacy rates range from 25% to 80%, with most drugs falling in the range of 50 to 60%.[5] For example, only 50-60% of patients experience improved outcome with drug therapy used for depression, schizophrenia and cardiac arrhythmias (Table 1).[8]

Table 1: Drug Efficacy Rates For Major Drugs in Selected Therapeutic Areas

Therapeutic Area	Efficacy rate (%)
Cardiac arrhythmias	60
Schizophrenia	60
Depression (SSRI)	62
Analgesics (Cox-2)	80

Genetic Variation and Adverse Drug Reactions (ADR)

Adverse drug events due to variability in drug responses are often preventable[9] and remain an underappreciated clinical issue. The Food & Drug Association Adverse Events Reporting System (FAERS) estimated 800,000 ADRs in the U.S. and Europe combined for the year 2011.[10] The incidence of serious & fatal ADRs has been rising with the increase in the number of medications prescribed. An estimated $3.5 billion is spent on additional medical cost associated with ADRs annually and at least 40% of this may be preventable.[11]

Cytochrome P450 2D6 (CYP2D6) Enzyme

Drugs may be metabolized by more than one pathway involving several enzymes of the cytochrome P450 class. Cytochrome P450 enzyme 2D6 (CYP2D6) alone is thought to be active in the enzymatic breakdown of 20-25% of all medicines prescribed[12] including antidepressants, antipsychotics, opioids, beta-blockers, antiarrhythmics, and the drug tamoxifen.

Genetics of CYP2D6

Most individuals have two CYP2D6 alleles, one inherited from each parent. The combination of these two alleles ('genotype') determines the overall level of CYP2D6 enzyme activity, or phenotype, particular to that combination.

Cytochrome P450 2C19 (CYP2C19) Enzyme

Cytochrome P450 enzyme 2C19 (CYP2C19) metabolizes many clinically important drugs including proton pump inhibitors, antidepressants, the antiplatelet drug clopidogrel, and the antifungal voriconazole.[13]

Genetics of CYP2C19

Like CYP2D6, most individuals are born with two CYP2C19 alleles The combination of these two alleles determines the overall level of CYP2C19 enzyme activity, or phenotype, particular to that combination.

The mutations in the CYP2C19 gene are heritable. Up to 34 different variations in the gene sequence have been described for CYP2C19.[14] The CYP2C19*1 allele is considered the wild-type, or "normal" allele, with "normal" enzyme activity.

Table 2: Prevalence of CYP2C19 Phenotypes in the General Population[15]

2C19 Phenotype	Percent of patients with phenotype
Extensive	35-50
Intermediate	18-45
Poor	2-15
Ultra-rapid	5-30

Conclusion

Laboratory techniques to detect drug response variability exist currently. Phenotyping and /or genotyping are primary methods used. Phenotyping is carried out by measuring enzyme activity directly using a probe drug whose metabolism is known to be solely dependent on the particular CYP enzyme. However, using a probe drug to measure individual phenotypes has limitations. Measuring concentration at various time points requires collecting multiple specimens at fixed times (typically at 8 hours post-administration). The individual is also exposed to possible unfavorable side effect of the probe-drug. Additionally, the metabolism of the probe drug may be affected by interfering drugs, disease status and other environmental factors (such as a patients overall health, weight, age, diet).

The drug-metabolizing phenotype of an individual can also be predicted using assays that determine genotype from a patient sample. Genotyping results are not affected by drugs, diet or environmental factors. Genotyping assays by molecular methods are fast, reliable and accurate. The interpretation of the genotype result to the phenotype is based mainly on literature, and on the physician's judgment.

Identification of patient genotypes for clinically relevant CYP genes can help physicians tailor drug treatment to patients through the selection of appropriate therapies. These measures may improve a physician's ability to impact patient outcome by ensuring maximum drug efficacy with minimal adverse drug reactions.[6]

xTAG CYP2C19 Kit v3 (EU-IVD) Intended Use

The xTAG CYP2C19 Kit v3 (EU-IVD) is an in vitro diagnostic test used to simultaneously detect and identify a panel of nucleotide variants found within the highly polymorphic CYP450 2C19 gene, located on chromosome 10q24, from genomic DNA extracted from EDTA or citrate anticoagulated whole blood samples.

The xTAG CYP2C19 Kit v3 is a qualitative genotyping assay which can be used as an aid to clinicians in determining therapeutic strategy for the therapeutics that are metabolized by the CYP2C19 gene product, specifically *1, *2, *3, *4, *5, *6, *7, *8, *9, *10, and *17.

This kit is not indicated for stand-alone diagnostic purposes. The information provided from this test may supplement decision making and should only be used in conjunction with routine monitoring by a physician. Because of the variability in the knowledge of clinical utility with specific drugs that are metabolized by CYP2C19, clinicians should use professional judgment in the interpretation of results from this test. Results from this type of assay should not be used in predicting a patient's response to drugs for which the drug metabolizing enzyme activity of that allele, or the drug metabolic pathway, has not been clearly established.

xTAG CYP2D6 Kit v3 (EU-IVD) Intended Use

xTAG® CYP2D6 Kit v3 is a device used to simultaneously detect and identify a panel of nucleotide variants found within the highly polymorphic CYP2D6 gene located on chromosome 22 from genomic DNA extracted from EDTA and citrate anticoagulated whole blood samples. This kit can also identify gene rearrangements associated with the deletion (*5) and duplication genotypes. xTAG CYP2D6 Kit v3 is a qualitative genotyping assay which can be used as an aid to clinicians in determining therapeutic strategy for therapeutics that are metabolized by the CYP2D6 gene product. This kit is not indicated for stand-alone diagnostic purposes. This test is not intended to be used to predict drug response or non-response.

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