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## Word from the President

### Prof. Han van Krieken



Dear Members,

We are now three months after the superb congress in Lisbon, and I hope your memories to that meeting are as good and vivid as mine. The last weeks we have been already very busy with the program for our next meeting in London, and the working groups really made efforts to even improve! I am now also 3 months in office and come to realize more and more how well my predecessors have worked, especially the immediate past-president Fatima Carneiro has done so much for our society that we cannot thank her enough!

Pathology is changing fast. In Lisbon we discussed in several sessions how important it is to perform RAS testing in colorectal cancer rather than KRAS testing. Shortly after the meeting the New England Journal of Medicine published the data we discussed and the EMA altered the label for one of the EGFR targeting drugs, implying a rapid change in our practice. And last week the EMA did the same for the other EGFR targeting drug. This means that now we cannot do KRAS testing alone anymore, since those patients who have a NRAS mutated tumor do actually worse upon EGFR targeted treatment.

This is an example how our profession is changing fast: we are expected to change our way of testing virtually overnight. I am glad that in Lisbon we could inform our members how important it is to be prepared. But it leaves me also with a question: do we do enough? How can we as ESP reach out to make everybody prepared? Would you like that the ESP sends out a letter in such a case where our practice has to change immediately.

I received many positive comments on our new website, although it is not yet completely as we like it to be. I hope you had the opportunity to look at it and at the educational material. I think that this is another extra tool that we can use in our practice. Of course the ESP welcomes you criticism, suggestions, ideas to improvement. One point was not good: online payment of the fees was not possible, a really nuisance and you were to complain. This is now solved for the time being. We will make further improvements, but that will take time.

Here, the days are getting shorter, which means that we are approaching the end of the year. Again a year in which much happened. In several countries the economical crises makes life difficult for many, and also pathology is affected by austerity. I hope you are all able to keep your enthusiasm for our wonderful profession. I wish you a good holiday season in which you can enjoy good moments with your loved ones, have moments to reflect on the past year and make plans for the New Year. I do hope that 2014 will bring everything you hope for.

Han van Krieken



**Word from the Editor  
Prof. Aurelio Ariza**



Dear colleagues,

After the conscientious and excellent work of Dr. Loukas Kaklamanis as editor of our Newsletter, it is now my turn to relieve him and carry on the editing task with the invaluable aid of Krasi Serguieva. Dr. Kaklamanis, however, does not leave our pages. He will continue to enrich each issue with his *Analecta Medica*, that prodigious summary of what is going on in the world of science and medicine and one of the more closely followed sections of the Newsletter. Loukas, from all of us, thank you so much!

This Newsletter number 15 brings us Prof. Han van Krieken's salute as new president of the ESP and his thoughts on the accelerated changes our profession is experiencing. We wish him the best for his two-year term as helmsman of European pathology in a time of unique threats and unprecedented opportunities.

This issue also provides us with Prof. Fátima Carneiro and Prof. Manuel Sobrinho-Simões' powerful remembrances of the Lisbon 2013 European Congress of Pathology (ECP). Those warm late summer days, during which we European pathologists enthusiastically shared both science and friendship by the banks of the Tagus, are vividly brought to mind by their very telling words and pictures.

Afterwards, Prof. Fátima Carneiro and Prof. Manuel Sobrinho-Simões delve further into the past by reminding us of the London 1977 ECP in the "In illo tempore" section. What better viewpoint to contemplate the upcoming London 2014 ECP? In a likewise effort to set the stage for that most promising convergence of European pathologists by the banks of

the Thames, Prof. Ian Ellis depicts the main features of its host society, the Pathological Society of Great Britain and Ireland (aka Path Soc). The next issues of our Newsletter will further pave the way to the London 2014 ECP, so as to make it abundantly clear that hardly anyone may afford to miss it.

The following pages also contain Prof. Antonio López-Beltrán's words on the Uropathology Working Group (WG) of the ESP. As chair of that WG, he updates us on its structure, describes the activities held in 2013, and shares with us his ambitious projects for 2014 and beyond.

Pathology national societies are the bones of the ESP, whereas WGs are its muscles. As such, gradual identification of national societies with the ESP and steady fortification of ESP WGs are to be pursued in earnest. Our Newsletter will continue to give prominence to the various national societies and ESP WGs in order to foster unrelenting progress in that direction.

But no true cohesion of European pathology will be attained without the harmonisation of the different countries' training programmes. A strategic goal in that regard is the harmonisation of the end-product quality, for which a progress test for pathology trainees has been developed. In his concluding article, Prof. Fred T. Bosman gives us the gist of it and masterly outlines the dreams and realities of pathology training in a European context.

Best wishes for the holidays and please stay tuned for all the interesting news we'll bring you in 2014!

Aurelio Ariza



## **Urothology Working Group of the ESP: activities held in 2013 and planned for 2014**

### **Prof. Antonio López-Beltrán, Chair**

The Urothology Working Group (WG) of the ESP has been quite active during 2013. Election of a new WG chair has inaugurated a new period, during which Prof Montironi, Prof Algaba, Prof Martignoni and Prof Hartmann will accompany the chair as advisory board officials.

The main efforts of the Urothology WG in 2013 have concentrated on the organization of scientific activities at the Lisbon European Congress of Pathology (ECP). These activities included a joint symposium of the ESP Urothology WG and the International Society of Urological Pathology; a short course entitled Urologic Oncology Update; a slide seminar; and a video-microscopy session. Speakers at the symposium and short course, selected among the most active European and American urothologists, provided a most inspiring overview on recent developments in the field.

As for the slide seminar and video-microscopy speakers, they were chosen among young European pathologists who had expressed their wish to participate in the events. It is the agreement of the Urothology WG scientific committee that slide seminars and video-microscopy sessions should be entrusted to young European pathologists with interest in the field, as a way to stimulate their active participation in ESP activities and foment their interest in urothology.

The WG chair has already provided the urothology contents and speakers for the London 2014 ECP. Activities in London will include a joint meeting of the ESP Urothology WG and the International

Urothology WG and the International Society of Urological Pathology on recent advances in urologic cancer; a short course on the art and science of urothology; and a slide seminar on tumour-like conditions in urothology. In addition, the London 2014 ECP will witness the first ever joint meeting of the Urothology and Gynecological Pathology WGs of the ESP, which will discuss topics at the border zone between both subspecialties. Currently, the WG chair and officials are working on the urothology activities to be held at the Belgrade 2015 ECP, with the goal of completing their planning by the spring of 2014.

Other activities developed in 2013 by members of the ESP Urothology WG include the participation in the Vancouver Consensus Conference on Renal Cancer and the Consensus on Best Practices of Immunohistochemistry in Urothology. The proceedings of those activities have been published in widely diffused pathology and urology journals.

Finally, WG board members will hold a joint meeting with urologists at the European Association of Urology congress in Stockholm in 2014. Likewise, an update course on urothology, jointly organized by the ESP Urothology WG and the Turkish Society of Pathology, will be held on 23-24 May 2014 in Ankara, Turkey.

Antonio López-Beltrán



## The Pathological Society of Great Britain and Ireland

### Prof. Ian Ellis, President

The Pathological Society of Great Britain and Ireland is the professional organisation supporting academic pathology in the UK and is dedicated to enhancing high quality research and education in pathology in its broadest sense. The stated focus and mission of the Pathological Society is to promote the understanding of disease and the Society actively engages with other organisations and in partnership to develop programmes to achieve this goal. We are delighted that *Understanding Disease* has been adopted as the motto of London 2014 our joint meeting with the European Society of Pathology. This mission encompasses the support and encouragement of research and other activities that further the understanding of disease mechanisms and processes, with resultant patient benefit, as well as the support for educational activities that promote the *Understanding of Disease* by all, including the general lay public.

The Pathological Society of Great Britain and Ireland was founded in 1906 and enjoyed its centenary in 2006 when the celebrations included publication of a monograph detailing its history

<http://www.pathsoc.org/index.php/about/history-of-the-pathological-society> Its first meeting was held in Manchester on 14<sup>th</sup> July 1906 when 17 papers and 31 demonstrations (by 17 demonstrators) were given.

The first paper on the agenda was by James Ritchie one of the recognized founders of the Society. It is noteworthy that the stated background to its formation was the observation that “the nineteenth century, and especially its first three-quarters, was teeming with pathological activity, and we may well consider that in this period the science of pathology, if not founded, certainly came to recognition as a branch of science with a defined place, distinct from the clinical arts.”

Membership of the Society, often referred to as Path Soc, is open to all individuals involved in pathological research and education and includes the option of a subscription to our Society Journal. The Journal of Pathology is one of the foremost and highest impact journals in the field. Path Soc currently hosts a major conference twice a year with outstanding speakers on a range of topics from basic molecular pathology to diagnostic practice and provides a forum for investigators across the world to present their research. The Society also has a generous range of grants that it awards to its members including PhD studentships, scholarships and travel support. It aims to facilitate future high quality research, by developing programmes for undergraduate and postgraduate teaching, and by engaging with the general public.

The membership of the Society is mainly drawn from the UK but also includes a significant international membership. Members are a mixture and clinical and experimental pathologists. There is a strong representation of academic pathologists within the membership. A flourishing Trainees Group operates within the membership and represents those who are in the process of training in the discipline of pathology. The Society is run by a Committee elected from its membership. A group of Officers of the Society manage executive functions. These include a President (currently Ian Ellis), a General Secretary (Richard Byers), a Treasurer (Nick Rooney) and a Meetings Secretary (Adrienne Flanagan). Several sub-committees advise the main Committee, especially in developing research, education & training.

Ian Ellis

encompasses 23 topics, four Keynote Lectures and several Special Sessions.

One thousand four hundred and thirty (1430) abstracts were submitted (8% increase compared to ECP 2012). Of the 1430 submissions, 182 were accepted for oral presentation (18 sessions) and 1072 for poster presentation (25 sessions). The number of no-shows was minimal and the great majority of the Working Groups did a very good job regarding the on site discussion of the posters. Prizes were given to the three best posters and the three best oral free papers.

## 25th European Congress of Pathology Lisbon 2013

Prof. F. Carneiro and Prof. M. S. Simões

The 25th European Congress of Pathology (ECP 2013) was held in Lisbon from August 31th to September 4th, 2013.

The ECP 2013 was organized by the European Society of Pathology (ESP) and the Portuguese Society of Pathology/Portuguese Division of the International Academy of Pathology and took place in the extremely nice and adequate Lisbon Congress Center that was also responsible for the highly appreciated catering. Besides the food, the site and the organization including internet connection, time schedule and projection details were classified as very good or excellent by the large majority of the participants.

The ECP 2013 was attended by 2182 delegates – a record in European Congresses of Pathology in the last years. There were 223 accompanying persons and 313 registered members of the Exhibition/Sponsors teams, leading to a total number of 2718 registered participants.

The 2182 delegates came from 81 countries (curiously, in the first count there were 82 countries because a pathologist registered as being from Scotland). The top 10 countries were the following: Portugal (n=184), Spain (n=127), United Kingdom (n=126), Russia (n=110), Greece (n=107), Turkey (n=98), The Netherlands (n=93), Germany (n=89), USA (n=81) and Brazil (n=80).

The *motto* of the ECP 2013 “Pathology: a gate to the future” was symbolically represented by the icon of the Congress: The Tower of Belém, a monument close to the congress center that commemorates the voyage to the unknown of the Portuguese navigators. The *motto* and the notion that Pathology, in addition to its traditional clinical problem solving role is entering uncharted waters, were strongly reflected in the scientific program that was prepared mainly by the ESP Working Groups and

### Winners of the Best Oral Free Papers



Timo Gaiser



Matthias Dettmer



Christian Schürch

The scientific program was organized daily in eight parallel sessions encompassing 23 Symposia, 10 Short Courses, 14 Slides Seminars, 8 Business Meetings together with scientific activities and 6 Videomicroscopy Sessions. The Keynote Lectures, the General Assembly and the Closing Ceremony which included the Residents Slide Seminar and the presentation of the three best oral free papers were held as Plenary Sessions. The four Keynote Lectures were the following: 1 – “Hallmarks of cancer: Applications to cancer medicine?” (Douglas Hanahan); 2 – Symeonidis Lecture: “A lifetime of morphological diagnosis” (Sebastian Lucas); 3 – “Clinical cancer genomics: A paradigm shift in medicine and pathology” (Carlos Caldas); 4 – “Haematopathology: The cutting edge of molecular pathology” (Elias Campo).

### Key note lecturers



Continues from p.6

Besides participating actively in the design of the scientific and social program of the Congress, the Portuguese Society of Pathology/Portuguese Division of the International Academy of Pathology has specifically organized, together with the Residents of 12 Portuguese Departments of Pathology, the Residents Slide Seminar that had been running in the internet for 6 months allowing the visualization of 24 cases that were eventually discussed by Juan Rosai and Ales Ryska.

#### Resident Slide Seminar



The Portuguese Society of Pathology has also organized three Special Sessions: the commemoration of the 150th Anniversary of the creation of the Pathology Chairs in Coimbra, Lisbon and Porto by D. Luis I, king of Portugal (co-chairs: Llobart Bosch and Daniel Serrão) and the commemoration of the 50th anniversary of the foundation of the ESP (co-chairs: Dusan Ferluga and Jan Vincent Johannessen) as well as two Sessions under the theme “The best of histopathology clubs” and “The best of molecular pathology in routine diagnosis”.

Among the Special Sessions, several were jointly organized by the ESP and the following international societies/associations: International Academy of Pathology (IAP), European Organisation for Research and Treatment of Cancer (EORTC), European Society of Medical Oncology (ESMO), United European Gastroenterology (UEG), European Association of Pathology Chairs and Program Directors (EAPCP) and Arthur Purdy Stout Society.

Finally, there were five Satellite Symposia organized by the Industry either at lunch time or even, in one case, at breakfast.

Following the *motto* of the Congress, a particular attention has been paid to the Residents who have organized the Plenary Slide Seminar and participated in the organization of some other scientific activities. The involvement of the Residents was crucial for obtaining the number of signatures necessary for the Proxy to the ESP Officers to represent the ESP members in the official registration of the new Statutes of the ESP. Together with the Local Organization Committee the Residents were also involved in the organization and running of some of the Social Events of the Congress and they were the stars of the Sunset Rave Party – Residents Night – on Sunday evening.

#### Sunset Rave Party



Like in other events of the Social Programme (see below), the full attendance of the Rave Party was attained and we felt very sorry for not being able to extend the “numerus clausus”. The Opening Ceremony was devoted to FADO with a talk by Rui Vieira Nery and a performance by Carminho, one of the most brilliant “fadistas” of the new generation.

#### Opening Ceremony with FADO



On Sunday we had the Sunset Rave Party, on Monday there was a concert in the São Carlos National Theatre with the Gulbenkian Foundation choir conducted by maestro Jorge Matta, and on Tuesday the President of Lisbon City Hall and the President of the ESP invited the Officers and Past-Officers of the Society and of the other Societies for a Presidential Dinner in Lisbon Town Hall.

#### Presidential Dinner



## Closing Ceremony



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On Wednesday night there was the Congress Party at Pátio da Galé in Terreiro do Paço of Lisbon with the performance of the TUNAS (masculine and feminine) of the Medical Faculty of the University of Porto. We felt again very sorry for not being able to accommodate more than the 550 places available.

### TUNAS performance at the Congress Party in Pátio da Galé



At the General Assembly the proposal of the Executive Committee to give the honorary membership of the ESP to Fred Bosman was unanimously approved.

### Fred Bosman was approved as honorary member of the ESP



The new Statutes of our Society were also approved (they have been registered at a Belgian notary in Antwerp on September 30, 2013).

Besides other very important points (good financial health of the ESP, creation of an Educational Portal, positive evolution of Virchows Archiv, election of Pierre Bedossa as President-elect), Han van Krieken became the new President of the ESP (2013-2015).

The sites for the forthcoming Congresses of the ESP were decided. According to the previous approval at the General Assembly in Prague, the ECP 2014 will be held in London, and the ECP 2015 in Belgrade. The ECP 2016 will be organized in Köln together with the Germany Division of the IAP, the ECP 2017 is scheduled for Amsterdam and the ECP 2018 will be held in Bilbao.

Although we realize our judgement is biased we think the Lisbon Congress of the ESP went very well from every standpoint (we do not know yet the financial details but we are confident the balance will be positive). The roles of Jorge Soares as chairperson of the Scientific Committee and of Rui Henrique as President of the Portuguese Society of Pathology were instrumental for the success of the meeting. We are convinced that a similar organizational model should be followed in the forthcoming ECPs – strong and coherent Organizing Committee in which both the ESP and the National Society(ies) of Pathology of the host country are represented.

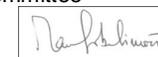
Among the few (and small) problems, those we think should be avoided in the future concern the distribution on time of the Abstract book and not to forget the “notebook and pen” in the elegant Congress bag (thank you Isabel Fonseca). With regard to the poster sessions, despite the improved situation in comparison with previous Congresses, we think it will be necessary to reinforce the participation of the representatives of the Working Groups and of the Poster presenters at the “on site” discussions.

We want to thank the other members of the Local Organizing Committee and the Scientific Committee, the ESP Officers and Administrator, the Chairpersons of the sessions, the active elements of the Working Groups and the secretarial assistance of Elisabete Pinto and Fátima Magalhães. We also want to thank the collaboration of CPO Hanser and the support of the Sponsors.

See you in August 30th, 2014, in London with a new version of the Lisbon Congress PIN.

Fátima Carneiro  
President of the ESP (2011-2013)

Manuel Sobrinho Simões  
Chair of the Local Organizing  
Committee



# Pathology newsletter

## In illo tempore: About the 6<sup>th</sup> ECP Congress Held in London in Sept 1977 and the Recruitment of UK Pathologists for the ESP

Prof. F. Carneiro and Prof. M. S. Simões

Since its birth in Brussels on March 1963 the ESP has tried to convince UK pathologists to join the Society. These efforts have not been particularly successful despite the major role played by Prof. Robert Scarf in the preparation, together with Profs Dustin, Giordano and Krauspe, of the Statutes and bylaws of the ESP.

In September 1967, out of the 190 ESP members, there were six pathologists from Great Britain and three from Ireland.

In the late sixties and early seventies, Profs. Dustin, Groniowski and Piringer-Kuchinka, Presidents of ESP, continued such efforts and in June 26, 1972, Prof. Swaen, Treasurer of the ESP, approached Prof. B. Moore, Secretary of the Pathological Society of Great Britain and Ireland: "For further information I have enclosed copies of some minutes, etc. of the previous meeting. As you will undoubtedly notice only a small part of the original high plans became a reality. I regret this very much and I hope that your countrymen will join the Society and will significantly contribute to realize some of the original intention".

At the General Assembly of the 4<sup>th</sup> ECP held in Budapest in September 1973 it was decided to hold in London, in 1977, the 6<sup>th</sup> ECP. "It was decided to hold the next Congress in Vienna, 1975. At the same time, the Assembly expresses the widest satisfaction for the willingness of the Colleagues of the Pathological Society of Ireland and Great Britain to host the 6<sup>th</sup> Congress in London, 1977. The Assembly has nevertheless underlined the need for an official invitation by the English Society. Should not this official invitation be sent, the European Society of Pathology will hold the 6<sup>th</sup> Congress in Brussels, following Prof. Dustin's proposal".

The Assembly took into consideration the site of the next Congress.  
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At the same time, the Assembly expressed the widest satisfaction for the willingness of the Colleagues of the Pathological Society of Ireland and Great Britain to host the 6th Congress in London, 1977. The Assembly has nevertheless underlined the need for an official invitation by the English Society. Should not this official invitation be sent, the European Society of Pathology will hold the 6th Congress in Brussels, following Prof. Dustin's proposal.  
The General Assembly then approved the applications for membership of 49 new members.  
The General Assembly ended at 3 p.m.  
The President  
The Secretary  
Giordano  
Piringer-Kuchinka

Prof. Nezelof has involved himself in the organization of the London Congress. In the letter he wrote to Prof. Swaen on May 3, 1976, Prof. Nezelof informs that "the negotiations about the programme with Prof. Munro Neville, President of the 6<sup>th</sup> ECP are progressing well". Curiously, in the same letter, Prof. Nezelof asks Prof. Swaen to correct the way his name is spelt in the letterhead of the ESP. "Puis-je vous demander de veiller à ce que sur les futurs papiers à en-tête de notre société, l'orthographe de mon soit respectée et que l'H disparaisse?"

The 6th ECP was held in London from September 11 to September 17, 1977 and encompassed five plenary sessions, 25 free paper sessions and 10 slide seminars.



The Congress was considered "very successful" by the officers and members of the ESP. Prof. Giordano, Secretary of ESP, provided a summary of this Congress in Pathol Res Pract 181, 472-479, 1986 and Prof. Nezelof offered Prof. Munro Neville, on behalf of the ESP, a silver plate. "Our London's Congress was I think very successful, due to the good organization of our President Munro Neville. At the end of the Apothecaries Banquet, in recognition of his effort, we offered him a small silver plate that he will keep as a souvenir of this congress. He looked very pleased with this present. The silver plate was purchased in London Silver Vaults. You will find enclosed a copy of the bill of this plate".

Besides agreeing with Prof. Nezelof opinion on the success of the Congress and letting him know the remittance of the amount spent on the gift, Prof. Swaen describes his attempts to recruit UK pathologists for the ESP. "Thank you for your letter. I agree with you that our London meeting was very well organized and certainly the president Munro Neville had earned himself a recognition of all the work he has done". ..... "I have sent to Prof. Munro Neville a proposal of a membership card and a letter for recruiting new members. I will wait for his comment. The adjusted text will be printed and sent to the participants of the London meeting inviting them to join our Society".

From the letter of Prof. Berry to Prof. Nezelof (August 29<sup>th</sup>, 1978) one guesses Prof. Berry has been a target of Prof. Swaen's attempt to recruit UK pathologists

The London Hospital Medical College  
University of London  
The London Hospital, London E1 1BB. Telephone 01-247 5454 Ext 267  
Department of Morbid Anatomy, Professor C. L. Berry, M.D., M.R.C. Path.  
29th August, 1978

Professor C. Nezelof  
European Society of Pathology  
Hospital Necker-Infirmerie Salpêtrière  
Service de Pathologie  
149 Rue de Sevres  
Paris  
France.

Dear Professor Nezelof,  
Despite writing on a number of occasions to the Secretary of the European Society I have not been asked to pay any subscription, nor received any information about the Society. I understand from colleagues, that I have been elected a member of the Society. I would be very glad if you could let me know who I should write to so I can resolve this difficulty.

Yours sincerely,  
C. L. Berry

Prof. Berry has become then a member of ESP and, later on, at the 1989 Porto Congress he was elected ESP President (1989-1991).

Fátima Carneiro  
Manuel Sobrinho Simões

Analecta Medica  
Dr. Loukas Kaklamanis



## 1) Paving the Way for Personalized Medicine – October 2013



### FDA's Role in a New Era of Medical Product Development

Over the past few years, a number of products that signal a new era of medical product development have entered the market or come on the horizon. In just the last two years, the FDA approved four cancer drugs for use in patients whose tumors have specific genetic characteristics that are identified by a companion diagnostic test. Last year, FDA approved a new therapy for use in certain cystic fibrosis patients with a specific genetic mutation. Earlier this year, three-dimensional (3D) printing was used to create a bioresorbable tracheal splint for treating a critically-ill infant. Each of these examples demonstrates the promise of “personalized medicine,” which is the tailoring of medical treatment to the individual characteristics, needs and preferences of each patient.

The concept of personalized medicine is not new: clinicians have long observed that patients with similar symptoms may have different illnesses, with different causes; and similarly, that medical interventions may work well in some patients with a disease but not in others with apparently the same disease. What is new is that advances in a wide range of fields from genomics to medical imaging to regenerative medicine, along with increased computational power and the advent of mobile and wireless capability and other technologies, are allowing patients to be treated and monitored more precisely and effectively and in ways that better meet their individual needs. Long before I became commissioner, FDA was attuned to the promise and potential challenges of personalized medicine. As a result of this forward thinking, the Agency moved quickly to build and shape a regulatory infrastructure to help make personalized medicine possible. I have made it a priority to continue to evolve FDA's regulatory processes in response to—and in anticipation of—scientific developments that are critical for the development of personalized therapeutics and diagnostics.

I am pleased to offer this report, *Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development*, as part of the Agency's ongoing commitment to this important and emerging area of medicine. The report describes the ways in which FDA has worked to respond to, anticipate and help drive scientific developments in personalized therapeutics and diagnostics. For the first time, it provides a compendium of FDA's many recent efforts to advance regulatory standards, methods and tools in support of personalized medicine and to further refine critical regulatory processes and policies in order to bring about personalized medical product development. This thoughtful report should serve as a useful resource for those looking toward a future where all stages of patient care—from prevention to diagnosis to treatment to follow-up—are truly personalized.

Margaret A. Hamburg, M.D. Commissioner of Food and Drugs

## 2) Bypass Mechanisms of Resistance to Receptor Tyrosine Kinase Inhibition in Lung Cancer

Matthew J. Niederst<sup>1,2</sup> and Jeffrey A. Engelman<sup>1,2\*</sup>

www.SCIENCESIGNALING.org 24 September 2013 Vol 6 Issue 294 re6

Receptor tyrosine kinases (RTKs) are activated by somatic genetic alterations in a subset of cancers, and such cancers are often sensitive to specific inhibitors of the activated kinase. Two well-established examples of this paradigm include lung cancers with either EGFR mutations or ALK translocations. In these cancers, inhibition of the corresponding RTK leads to suppression of key downstream signalling pathways, such as the PI3K (phosphatidylinositol 3-kinase)/AKT and MEK (mitogen-activated protein kinase kinase)/ERK (extracellular signal-regulated kinase) pathways, resulting in cell growth arrest and death.

Despite the initial clinical efficacy of ALK (anaplastic lymphoma kinase) and EGFR (epidermal growth factor receptor) inhibitors in these cancers, resistance invariably develops, typically within 1 to 2 years. Over the past several years, multiple molecular mechanisms of resistance have been identified, and some common themes have emerged.

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One is the development of resistance mutations in the drug target that prevent the drug from effectively inhibiting the respective RTK. A second is activation of alternative RTKs that maintain the signaling of key downstream pathways despite sustained inhibition of the original drug target. Indeed, several different RTKs have been implicated in promoting resistance to EGFR and ALK inhibitors in both laboratory studies and patient samples.

In this mini-review, we summarize the concepts underlying RTK-mediated resistance, the specific examples known to date, and the challenges of applying this knowledge to develop improved therapeutic strategies to prevent or overcome resistance.

3)



### Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update

Antonio C. Wolff,\* M. Elizabeth H. Hammond,\* David G. Hicks,\* Mitch Dowsett,\* Lisa M. McShane,\*  
Kimberly H. Allison, Donald C. Allred, John M.S. Bartlett, Michael Bilous,  
Patrick Fitzgibbons, Wedad Hanna,  
Robert B. Jenkins, Pamela B. Mangu, Soonmyung Paik, Edith A. Perez,  
Michael F. Press, Patricia A. Spears,  
Gail H. Vance, Giuseppe Viale, and Daniel F. Hayes

Published online ahead of print at [www.jco.org](http://www.jco.org) on October 7, 2013.  
\*Steering Committee member American Society of Clinical Oncology  
Clinical Practice Guideline Committee  
approval: April 26, 2013; College of American Pathologists approval: June 21, 2013.

#### Purpose

To update the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guideline recommendations for human epidermal growth factor receptor 2 (HER2) testing in breast cancer to improve the accuracy of HER2 testing and its utility as a predictive marker in invasive breast cancer.

#### Methods

ASCO/CAP convened an Update Committee that included coauthors of the 2007 guideline to conduct a systematic literature review and update recommendations for optimal HER2 testing.

#### Results

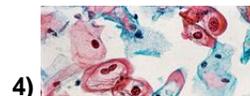
The Update Committee identified criteria and areas requiring clarification to improve the accuracy of HER2 testing by immunohistochemistry (IHC) or in situ hybridization (ISH). The guideline was reviewed and approved by both organizations.

#### Recommendations

The Update Committee recommends that HER2 status (HER2 negative or positive) be determined in all patients with invasive (early stage or recurrence) breast cancer on the basis of one or more HER2 test results (negative, equivocal, or positive). Testing criteria define HER2-positive status when (on observing within an area of tumor that amounts to  $\geq$  10% of contiguous and homogeneous tumor cells) there is evidence of protein overexpression (IHC) or gene amplification (*HER2* copy number or *HER2/CEP17* ratio by ISH based on counting at least 20 cells within the area). If results are equivocal (revised criteria), reflex testing should be performed using an alternative assay (IHC or ISH). Repeat testing should be considered if results seem discordant with other histopathologic findings. Laboratories should demonstrate high concordance with a validated HER2 test on a sufficiently large and representative set of specimens. Testing must be performed in a laboratory accredited by CAP or another accrediting entity. The Update Committee urges providers and health systems to cooperate to ensure the highest quality testing.

This guideline was developed through a collaboration between the American Society of Clinical Oncology and the College of American Pathologists and has been published jointly by invitation and consent in both *Journal of Clinical Oncology* and the *Archives of Pathology & Laboratory Medicine*.

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4)

### Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials

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The Lancet, Early Online Publication, 3 November 2013  
doi:10.1016/S0140-6736(13)62218-7 Cite or Link Using DOI

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## Summary

## Background

In four randomised trials, human papillomavirus (HPV)-based screening for cervical cancer was compared with cytology-based cervical screening, and precursors of cancer were the endpoint in every trial. However, direct estimates are missing of the relative efficacy of HPV-based versus cytology-based screening for prevention of invasive cancer in women who undergo regular screening, of modifiers (eg, age) of this relative efficacy, and of the duration of protection. We did a follow-up study of the four randomised trials to investigate these outcomes.

## Methods

176 464 women aged 20–64 years were randomly assigned to HPV-based (experimental arm) or cytology-based (control arm) screening in Sweden (Swedescreen), the Netherlands (POBASCAM), England (ARTISTIC), and Italy (NTCC). We followed up these women for a median of 6.5 years (1 214 415 person-years) and identified 107 invasive cervical carcinomas by linkage with screening, pathology, and cancer registries, by masked review of histological specimens, or from reports. Cumulative and study-adjusted rate ratios (experimental vs control) were calculated for incidence of invasive cervical carcinoma. **Findings**

The rate ratio for invasive cervical carcinoma among all women from recruitment to end of follow-up was 0.60 (95% CI 0.40–0.89), with no heterogeneity between studies ( $p=0.52$ ). Detection of invasive cervical carcinoma was similar between screening methods during the first 2.5 years of follow-up (0.79, 0.46–1.36) but was significantly lower in the experimental arm thereafter (0.45, 0.25–0.81). In women with a negative screening test at entry, the rate ratio was 0.30 (0.15–0.60). The cumulative incidence of invasive cervical carcinoma in women with negative entry tests was 4.6 per 105 (1.1–12.1) and 8.7 per 105 (3.3–18.6) at 3.5 and 5.5 years, respectively, in the experimental arm, and 15.4 per 105 (7.9–27.0) and 36.0 per 105 (23.2–53.5), respectively, in the control arm. Rate ratios did not differ by cancer stage, but were lower for adenocarcinoma (0.31, 0.14–0.69) than for squamous-cell carcinoma (0.78, 0.49–1.25). The rate ratio was lowest in women aged 30–34 years (0.36, 0.14–0.94).

## Interpretation

HPV-based screening provides 60–70% greater protection against invasive cervical carcinomas compared with cytology. Data of large-scale randomised trials support initiation of HPV-based screening from age 30 years and extension of

screening intervals to at least 5 years.

## Funding

European Union, Belgian Foundation Against Cancer, KCE-Centre d'Expertise, IARC, The Netherlands Organisation for Health Research and Development, the Italian Ministry of Health.

## 5)



## Economic burden of cancer across the European Union: a population-based cost analysis

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The Lancet Oncology, Volume 14, Issue 12, Pages 1165 - 1174, November 2013

## Summary

## Background

In 2008, 2.45 million people were diagnosed with cancer and 1.23 million died because of cancer in the 27 countries of the European Union (EU). We aimed to estimate the economic burden of cancer in the EU.

## Methods

In a population-based cost analysis, we evaluated the cost of all cancers and also those associated with breast, colorectal, lung, and prostate cancers. We obtained country-specific aggregate data for morbidity, mortality, and health-care resource use from international and national sources. We estimated health-care costs from expenditure on care in the primary, outpatient, emergency, and inpatient settings, and also drugs. Additionally, we estimated the costs of unpaid care provided by relatives or friends of patients (ie, informal care), lost earnings after premature death, and costs associated with individuals who temporarily or permanently left employment because of illness.

## Findings

Cancer cost the EU €126 billion in 2009, with health care accounting for €51.0 billion (40%). Across the EU, the health-care costs of cancer were equivalent to €102 per citizen, but varied substantially from €16 per person in Bulgaria to €184 per person in Luxembourg. Productivity losses because of early death cost €42.6 billion and lost working days €9.43 billion.

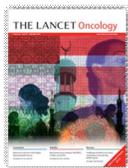
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Informal care cost €23.2 billion. Lung cancer had the highest economic cost (€18.8 billion, 15% of overall cancer costs), followed by breast cancer (€15.0 billion, 12%), colorectal cancer (€13.1 billion, 10%), and prostate cancer (€8.43 billion, 7%).

### Interpretation

Our results show wide differences between countries, the reasons for which need further investigation. These data contribute to public health and policy intelligence, which is required to deliver affordable cancer care systems and inform effective public research funds allocation.

6)



### Aurora kinases in head and neck cancer

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The Lancet Oncology, Volume 14, Issue 10, Pages e425 - e435, September 2013

In healthy cells, controlled activation of aurora kinases regulates mitosis. Overexpression and hyperactivation of aurora kinases A and B have major roles in tumorigenesis, and can induce aneuploidy and genomic instability. In squamous-cell carcinomas of the head and neck, overexpression of aurora kinase A is associated with decreased survival, and a reduction in aurora kinase A and aurora kinase B expression inhibits cell growth and increases apoptosis.

In this Review, we provide an overview of the biological functions of aurora kinases in healthy cells and in cancer cells, and we review small studies and high-throughput datasets that particularly implicate aurora kinase A in the pathogenesis of squamous-cell carcinomas of the head and neck. Early phase trials are beginning to assess the activity of small-molecule inhibitors of aurora kinases.

We summarise trials of aurora kinase inhibitors in squamous-cell carcinomas of the head and neck, and discuss directions for future drug combination trials and biomarkers to use with drugs that inhibit aurora kinases.

Loukas Kaklamanis



### Pathology training in a European context: dreams and realities. Prof. Fred T Bosman

University Institute of Pathology  
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Pathology training has long ago ceased to be a national affair. Many pathologists are practicing their specialty in a country other than that in which where they were trained. International mobility of medical practitioners is seen between European countries as well as transcontinental. The fact that the EU countries recognize each other's specialty diplomas and qualifications makes mobility within the EU relatively simple and so some European countries have an annual influx of foreign medical specialists exceeding 20% of their own 'production rate' of qualified specialists. By the way, this implies that some other European countries see their efforts to train qualified medical specialists part into thin air as a significant proportion of their 'end product' leaves the country! All this mobility is despite the fact that training programs in the countries in the EU are quite different, as has been published in a relatively recent survey [1], and training programs in anyone European country might not fully comply with the requirements for certification of a Medical Specialist in another European country.

The EU administration has deployed quite a bit of effort into getting to some level of harmonization, through the creation of the European Union of Medical Specialists (UEMS). This body has specialist sections, e.g. for Pathology the European Board of Pathology, with the intention to assure equal quality through harmonization of the different training programs.

Harmonization of training programs, however, has proved to be an illusion. Regulations are made at a national level and for the time being will remain the ultimate responsibility of national certifying bodies. There are no miracles. The Euro crisis has shown how far the EU is from integration in key socio-economic fields and Health Care is certainly among those for which national autonomy has remained the rule and this is unlikely to change in the foreseeable future. What the European Board of Pathology has attempted to do is create a set of basic rules in terms of the content of training programs, which serves as a very global definition of the qualities of the 'end product' of training programs in any EU country. This document has recently been validated and has been published [2]. In addition, the European Board of Pathology conducts an annual examination (The 'European Board of Pathology Examination'), a one day test usually conducted on site just before a European Congress of Pathology.

Continues from p.12

Participation in this examination, however, has been very low due to the fact that passing it does not confer to the successful participant any advantage in terms of securing employment. National regulations prevail!

Against this background some years ago the European Association of Pathology Chairs and Program Directors has been created in an attempt to implicate those specialist pathologists responsible for running an academic department and/or a training program in this harmonization effort. This group rapidly recognized that harmonization of training programs is an illusion. The only potentially useful contribution to attempts to harmonize the quality of the end-product has been the creation of a European progress test for pathology trainees. This goal was met with enthusiasm by a large group of pathology chairs and program directors and the project (EUROPALS) was financed by the EU and under the expert guidance of prof. Jan van den Tweel managed to provide a highly appreciated test over the last five years. Many of you will have seen the announcement of this test in the past month and quite a few of you have participated in this online test. The rules are simple: you register, get your own personal login, complete the test (which includes a number of cases to be diagnosed using virtual microscopy), participation is free, the result is anonymous (the individual participant gets individual feedback and results are not communicated to anyone else). A participant cannot 'pass' the test as it is anonymous. What it offers is an opportunity to compare own knowledge and diagnostic skills to that of peers. Over time, with recognition of the quality of the test and confirmation of its validity in terms of competency testing, the test might become one of the instruments certifying bodies in all EU countries use in the certification process. We will see how it evolves. The first attempt to have a test at a subspecialty level has also been successful with gastro-intestinal pathology as subspecialty field. For 2014 a subspecialty test will be run for lympho/hematopathology. The decision has been taken to incorporate these tests into the e-learning platform of the ESP, which is in full swing development. To stay informed, you should regularly consult the educational information on the ESP website.

#### References

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Fred T Bosman



### REDEFINING THE SPECTRUM OF SMALL B-CELL LYMPHOMAS IN LIGHT OF CURRENT TECHNOLOGY".

Information and Registration:

<http://www.eahp2014.org>

*Greetings Colleagues,*

*There is an exciting, new CME program sponsored by Beth Israel- A member of the Mount Sinai Health Care System taking place in Jerusalem, Israel in late October 2014. This event promises to be a rich combination of cutting-edge tutorials on GI pathology given by an international array of experts and local, cultural highlights. Please see our website: [www.gipathjerusalem.com](http://www.gipathjerusalem.com) for more details. Registration will begin in January 2014.*

*Best,*

Gabe Levi, MD  
Course organizer

Neil Theise, MD  
Course Director