DEP Lazio
Dipartimento di Epidemiologia del Servizio Sanitario Regionale Regione Lazio

SISTEMA SANITARIO REGIONALE
ASL ROMA E
REGIONE LAZIO

XXIV Seminario Nazionale
LA VALUTAZIONE DELL'USO E DELLA SICUREZZA DEI FARMACI: ESPERIENZE IN ITALIA
14 - 15 dicembre 2015

La medicina di precisione: implicazioni regolatorie e per la pratica clinica

Antonio Addis

forward01

Medicina di precisione

1999

Harold Varmus, direttore dei National Institutes of Health, invita i ricercatori statunitensi a sottoporre progetti di ricerca finalizzati a classificare i tumori in base alle caratteristiche molecolari e non morfologiche.

2000

THE HUMAN GENOMA PROJECT
The Human Genome Project viene completato.

2003

INDIVIDUALIZED MEDICINE
Utilizzato inizialmente in riferimento al metabolismo individuale del farmaco (Srivastava 2003), il termine è stato poi associato all'approccio terapeutico che prevede il ricorso a materiale cellulare per sviluppare una terapia mirata, p. es. *stem cell therapy* (Baker 2011) o vaccini oncologici (Gravitz 2011).

2004

PERSONALIZED MEDICINE
L'applicazione della farmacogenomica alla pratica clinica (Gupta 2004). Diventa il "termine ombrello" per un concetto sempre più utilizzato. L'anno successivo nasce la Personalized Medicine Coalition.

PMC
PERSONALIZED MEDICINE COALITION

2005

TREATING INDIVIDUALS
The Lancet pubblica una serie di cinque rassegne curate da Peter Rothwell che approfondiscono l'analisi per sottogruppi, ipotizzando la transizione "dai randomized controlled trials alla personalized medicine".

2007

STRATIFIED MEDICINE
Indica l'approccio basato sulle terapie capaci di andare incontro alle specifiche caratteristiche di pazienti utilizzando biomarker clinici (Trusheim 2007). Presuppone il ricondurre ogni malato ad una coorte o a una sottopopolazione di un insieme più ampio, dalle quali ci si attenda una diversa risposta alla terapia.

2008

P4 MEDICINE
Predittiva, personalizzata, preventiva e partecipata: ecco la medicina del futuro secondo Leroy Hood (2008). Driver di questa evoluzione: biologia molecolare, big data, social media e web.

2009

PRECISION MEDICINE
Introdotta per la prima volta nel 2009 (Boguski 2009) intendeva definire un modello che prevedesse
1. la conoscenza delle cause della malattia,
2. la capacità di identificare la presenza degli agenti causali e
3. la competenza/possibilità di intervenire efficacemente.

2011

La SM non si sviluppa solo a partire dalla genomica ma può fondarsi anche su altre discipline (p. es. l'imaging diagnostico) (Blair 2011).

Il report **Toward Precision Medicine** della US National Academy specifica ulteriormente il significato agganciandolo alla riclassificazione delle malattie su dati molecolari.

2012

Febbraio: una Perspective sul *New England Journal of Medicine* titola *Preparing for Precision Medicine*.

2015

A gennaio, nello State of the Union address, Barak Obama annuncia la Precision Medicine Initiative.

Francis S. Collins (direttore dei NIH) e Harold Varmus presentano la PM Initiative sul *New England*.

D/EP/Lazio

SISTEMA SANITARIO REGIONALE
ASL ROMA E
REGIONE LAZIO

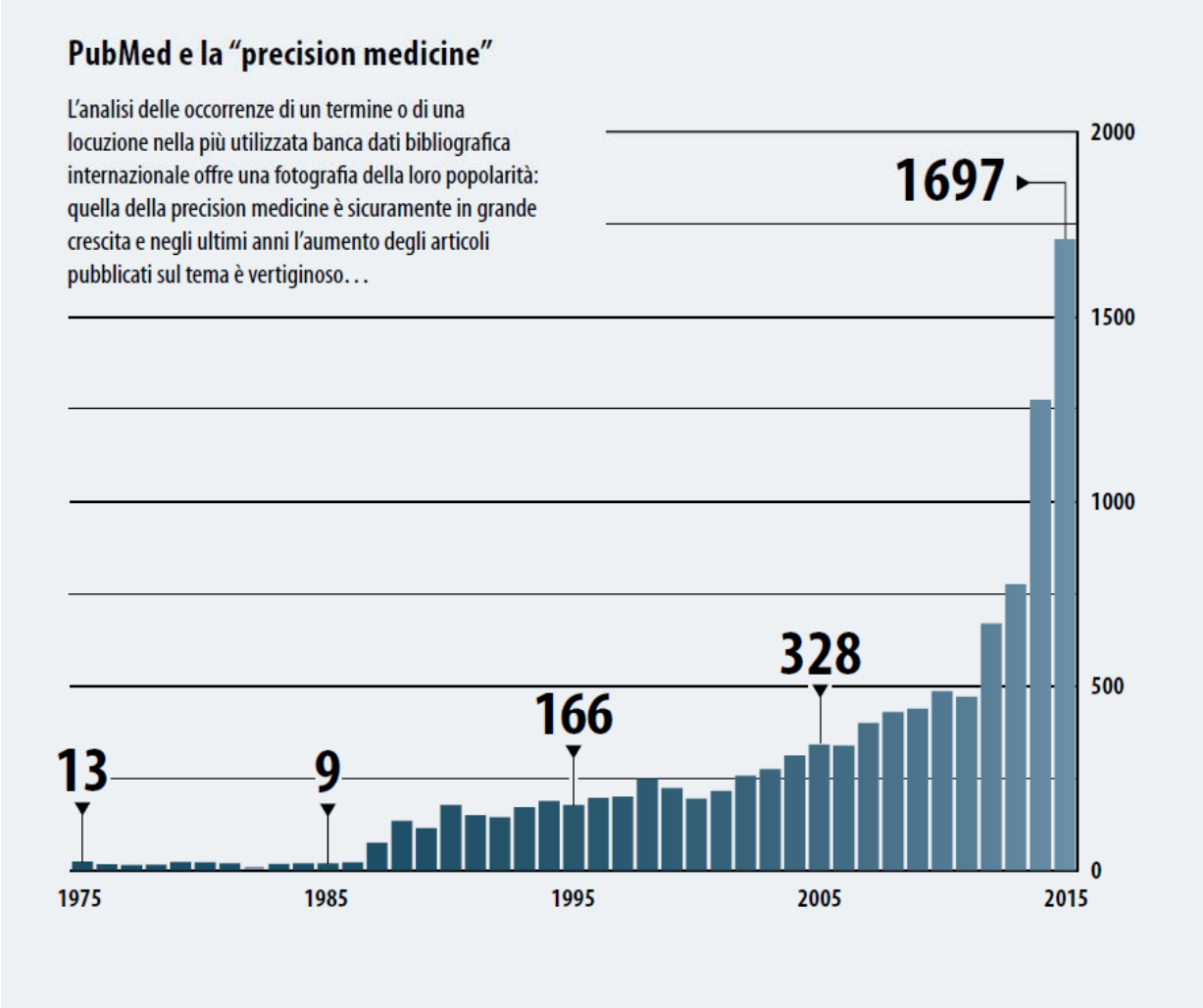
Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.

President Barack Obama, State of the Union Address, January 20, 2015

Il Pensiero ScientificoEditore
recentiprogressi.it/forward

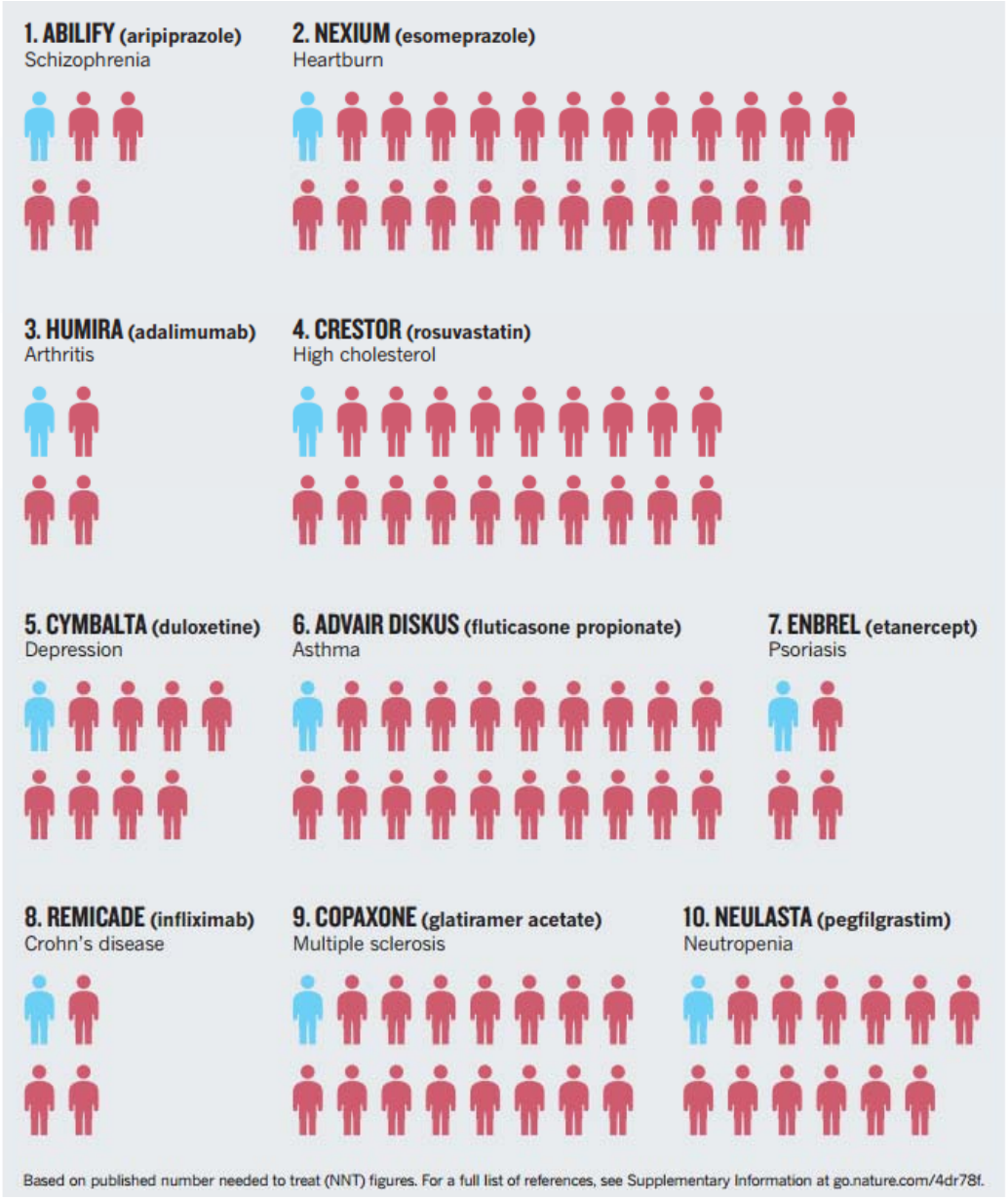
Medicina di precisione

forward



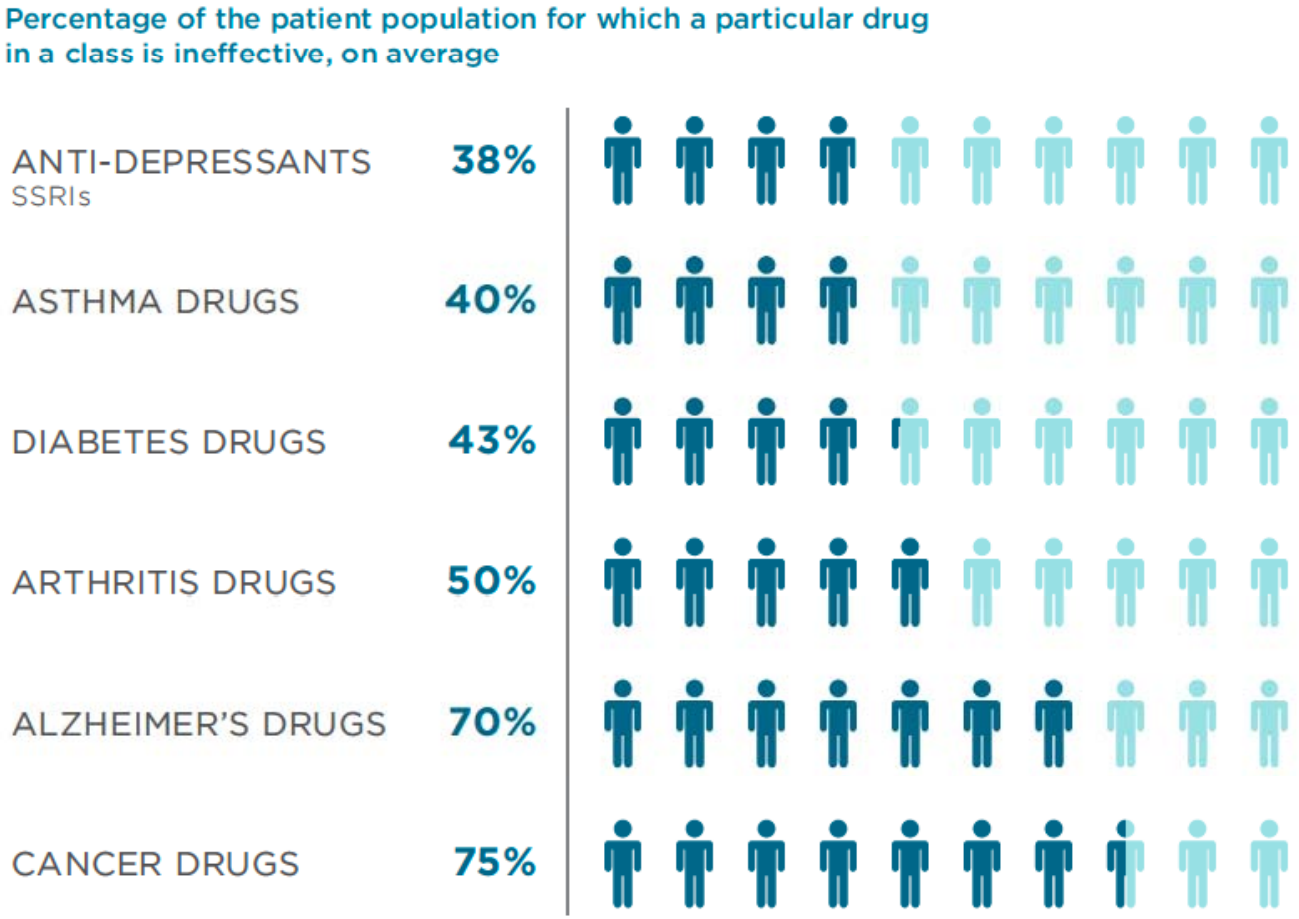
IMPRECISION MEDICINE

*For every person they do help (**blue**), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (**red**).*



30 APRIL 2015 | VOL 520 | NATURE | 609

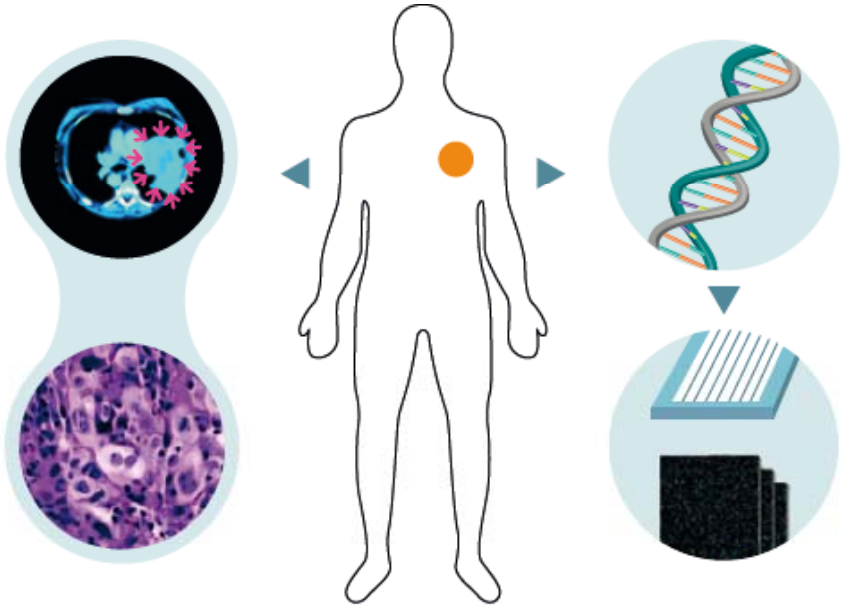
One size does not fit all



Source: Brian B. Spear, Margo Heath-Chiozzi, Jeffrey Huff, "Clinical Trends in Molecular Medicine," Volume 7, Issue 5, 1 May 2001, pages 201-204.

Figure 1. A Concept of Personalised Cancer Medicine.

On the left side, we can see a computed tomography (CT) scan showing a tumour in the lung. On the image below, a histological section is shown, basically representing how the pathologist sees the tumour tissue under the microscope. This panel is considered to be "classical" medicine in terms of the approach to treatment. On the right panel, we can see a schematic of molecular analysis of the tumour with possible findings: an actionable mutation and consequently treatment with an already approved drug or with a new drug within the context of a clinical trial. The findings could also indicate a prognosis or could be of non-significant relevance.



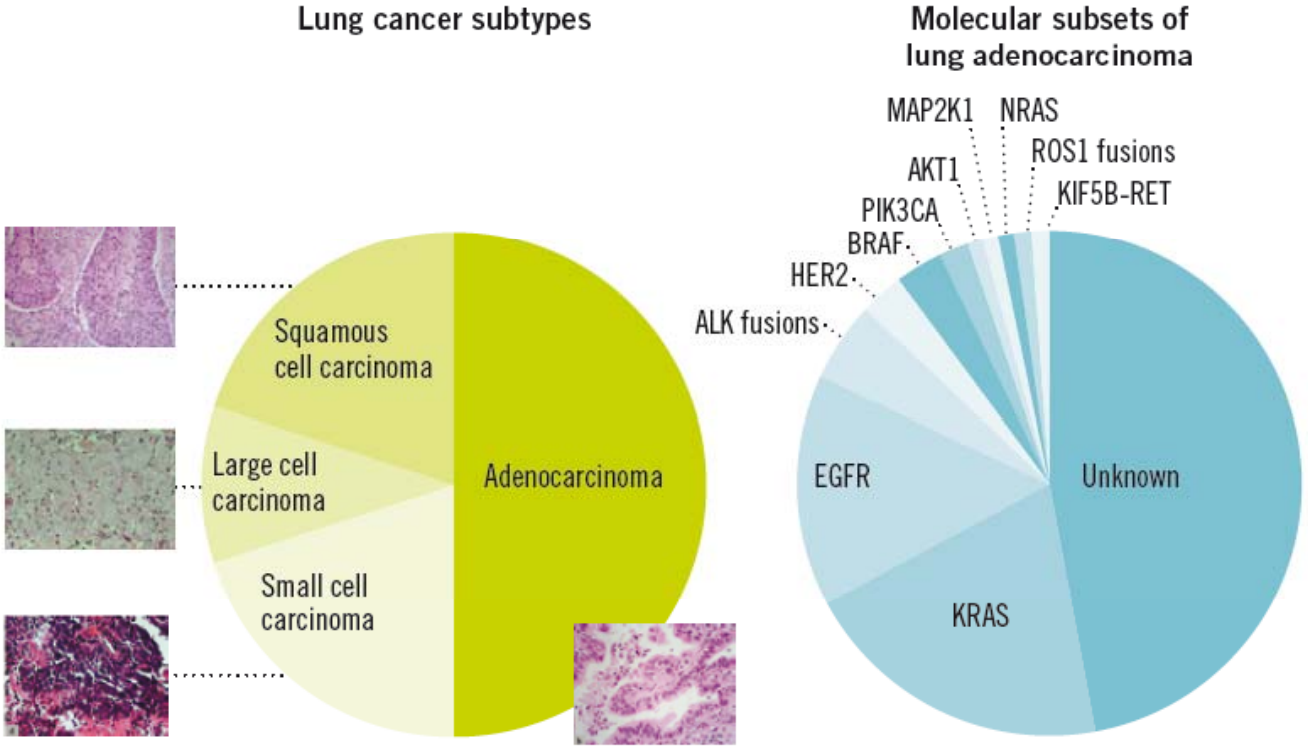
Category of Molecular Alteration
Actionable in principle **Situation 1:** Treatment with already approved drug **Situation 2:** Treatment with a new drug within a clinical trial
Prognostic
Variants of uncertain significance

Adapted from Garraway L *et al.* J Clin Oncol 2013; 31(15): 1803-1805, with permission.

Source: ESMO Patients Guide Series ESMO Personalised Medicine 2013

Figure 2. Lung Cancer – Not One Disease: Histological (Tissue) and Molecular Subtypes of Lung Cancer.

On the left side, four histological subtypes of lung cancer. On the right side, a pie chart showing the percentage distribution of molecular subsets of lung adenocarcinoma.

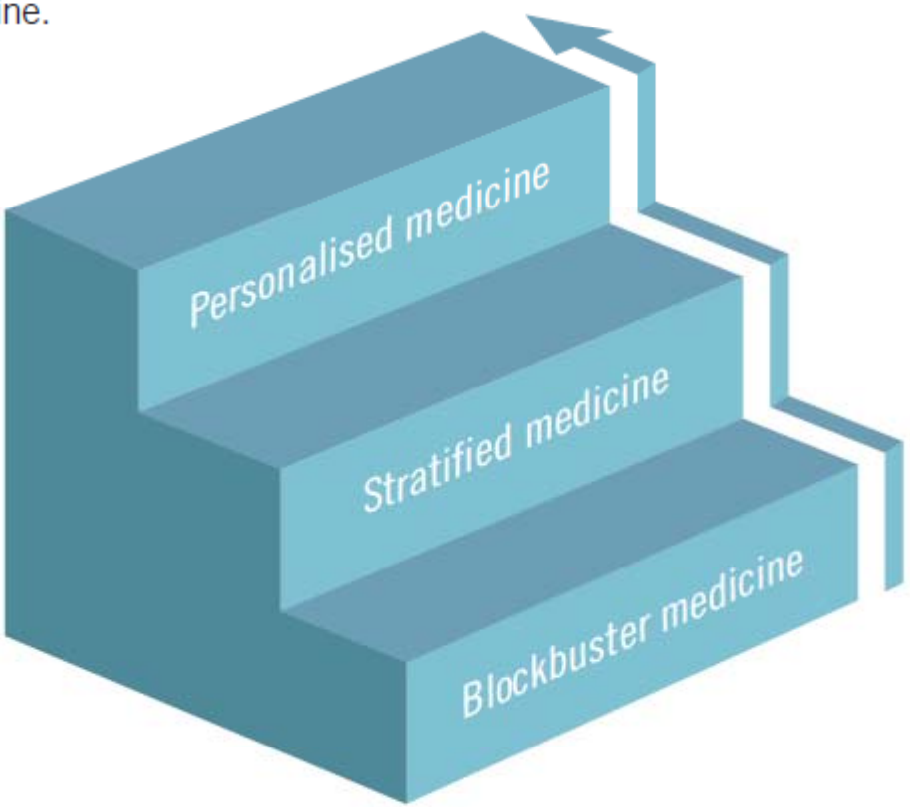


Adapted from Petersen I. Dtsch Arztebl Int 2011; 108(31-32):525-531 (left) and Pao W & Hutchinson KE. Nature Med 2012; 18(3): 349-351, with permission.

Source: from ESMO Patients Guide Series ESMO Personalised Medicine 2013

Figure 4. Personalised Medicine: A Stepwise Process.

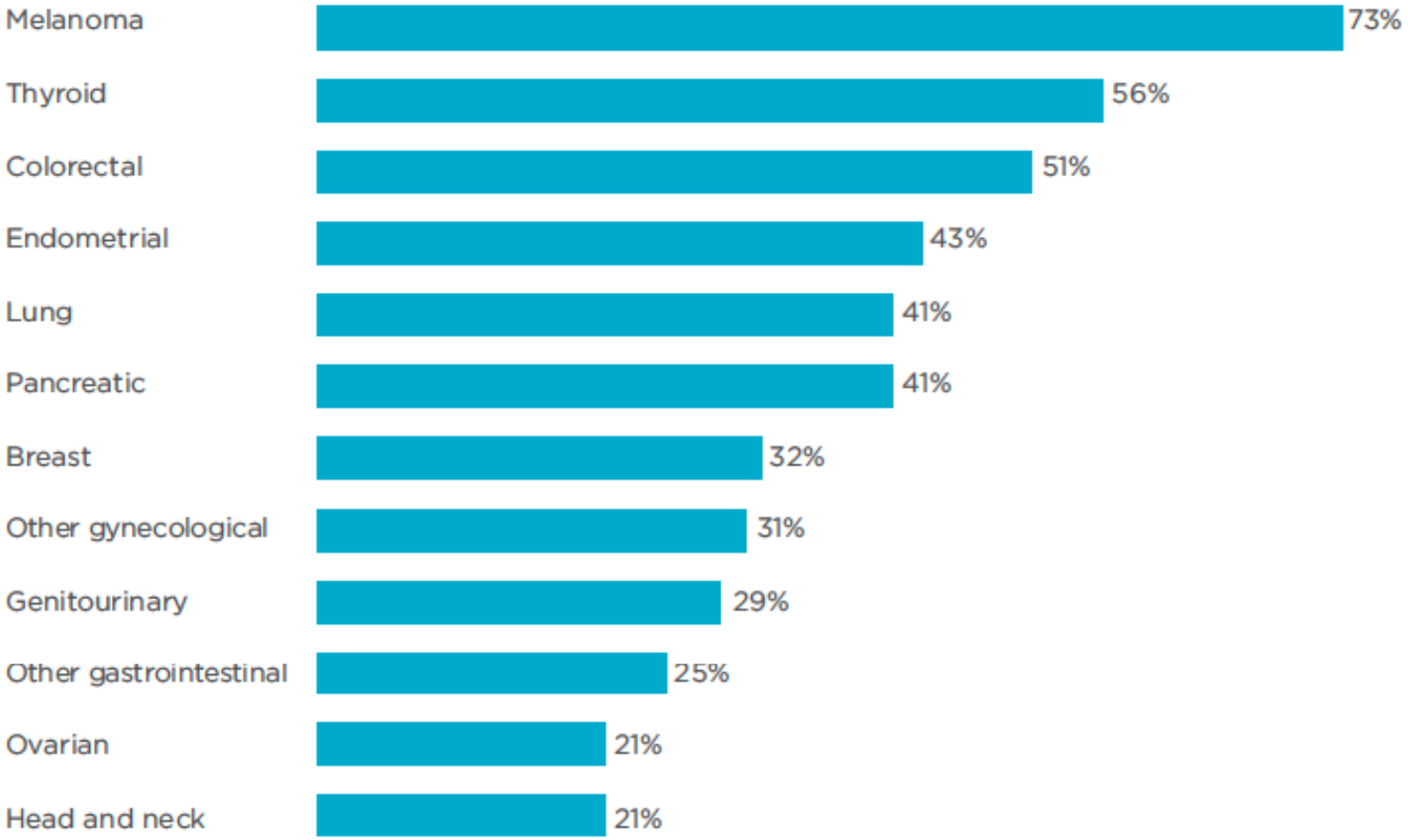
The move from blockbuster or empirical medicine* towards personalised medicine is a stepwise process. We are currently on the second step of stratified medicine and moving up the stairs towards personalised medicine.



Jørgensen JT. Expert Rev Mol Diagn 2008; 8: 689-695, with permission.

Source: from ESMO Patients Guide Series ESMO Personalised Medicine 2013

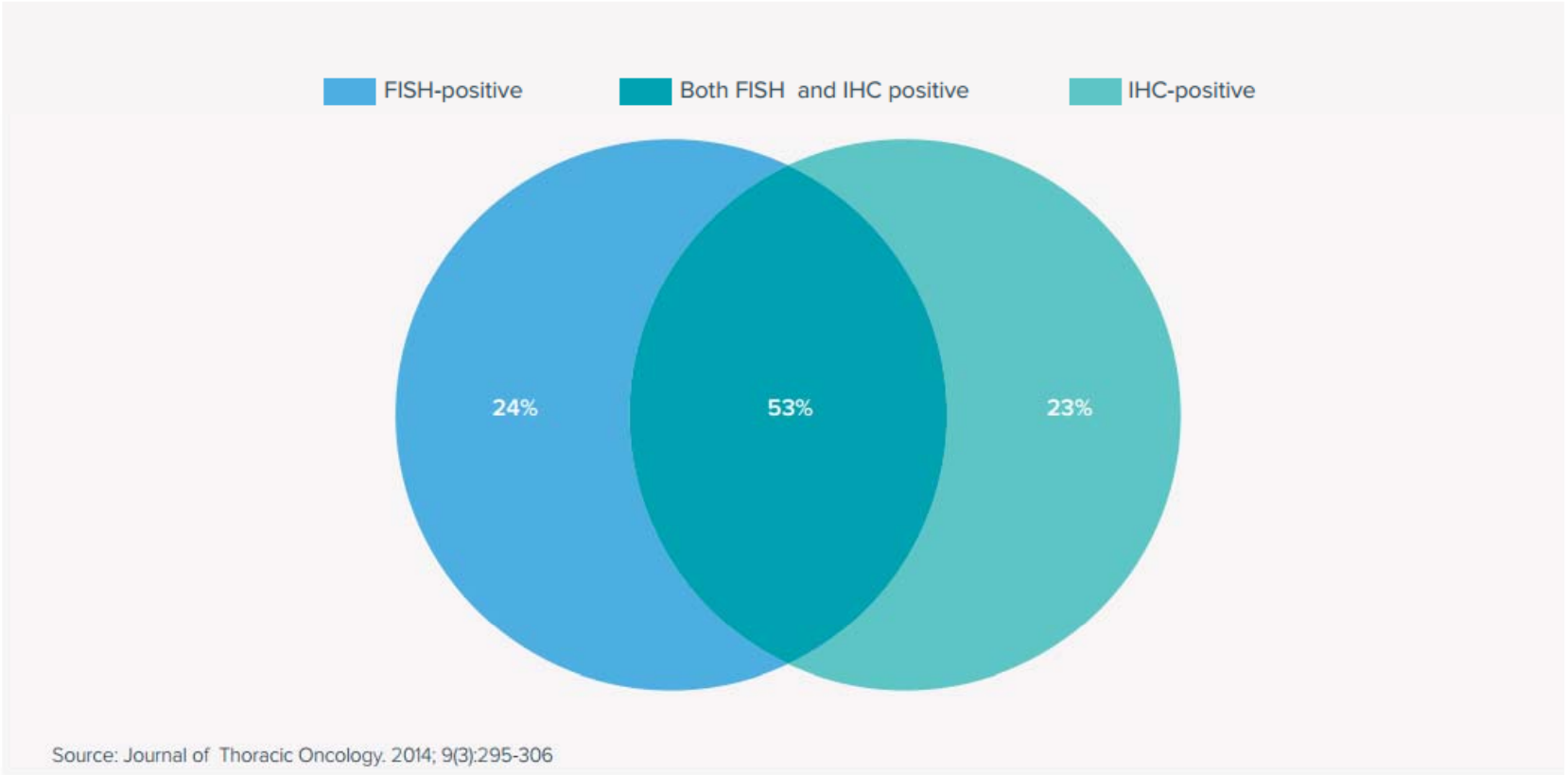
TACKLING TUMORS: Percentage of patients whose tumors were driven by certain genetic mutations that could be targets for specific drugs, by types of cancer.



Source: *Wall Street Journal* Copyright 2011 by DOW JONES & COMPANY, INC. Reproduced with permission of DOW JONES & COMPANY, INC.

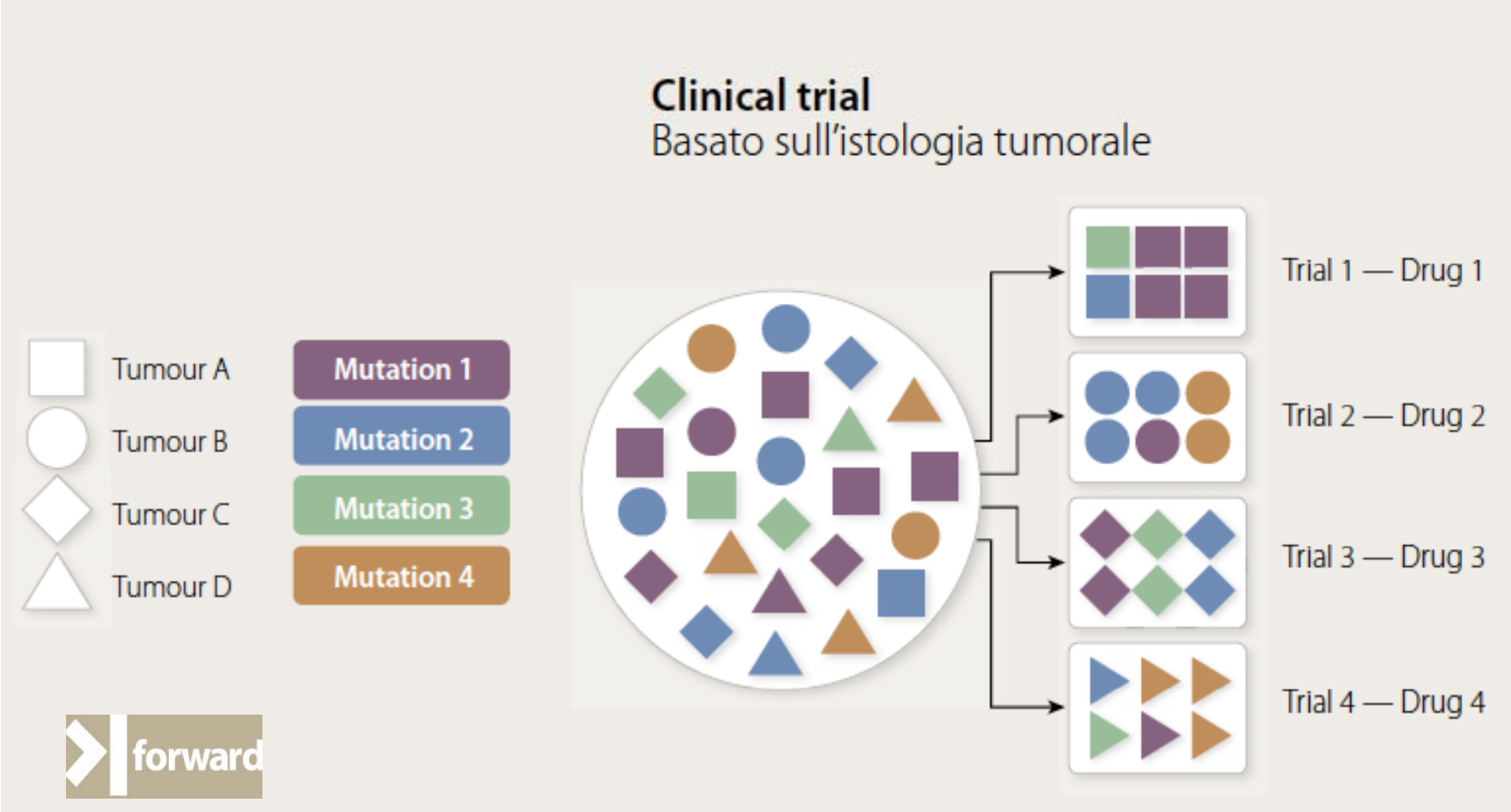
Biomarkers and companion diagnostics introduce complexity in part because of inconsistency in test results

Comparison of FISH and IHC Testing for ALK Rearrangements

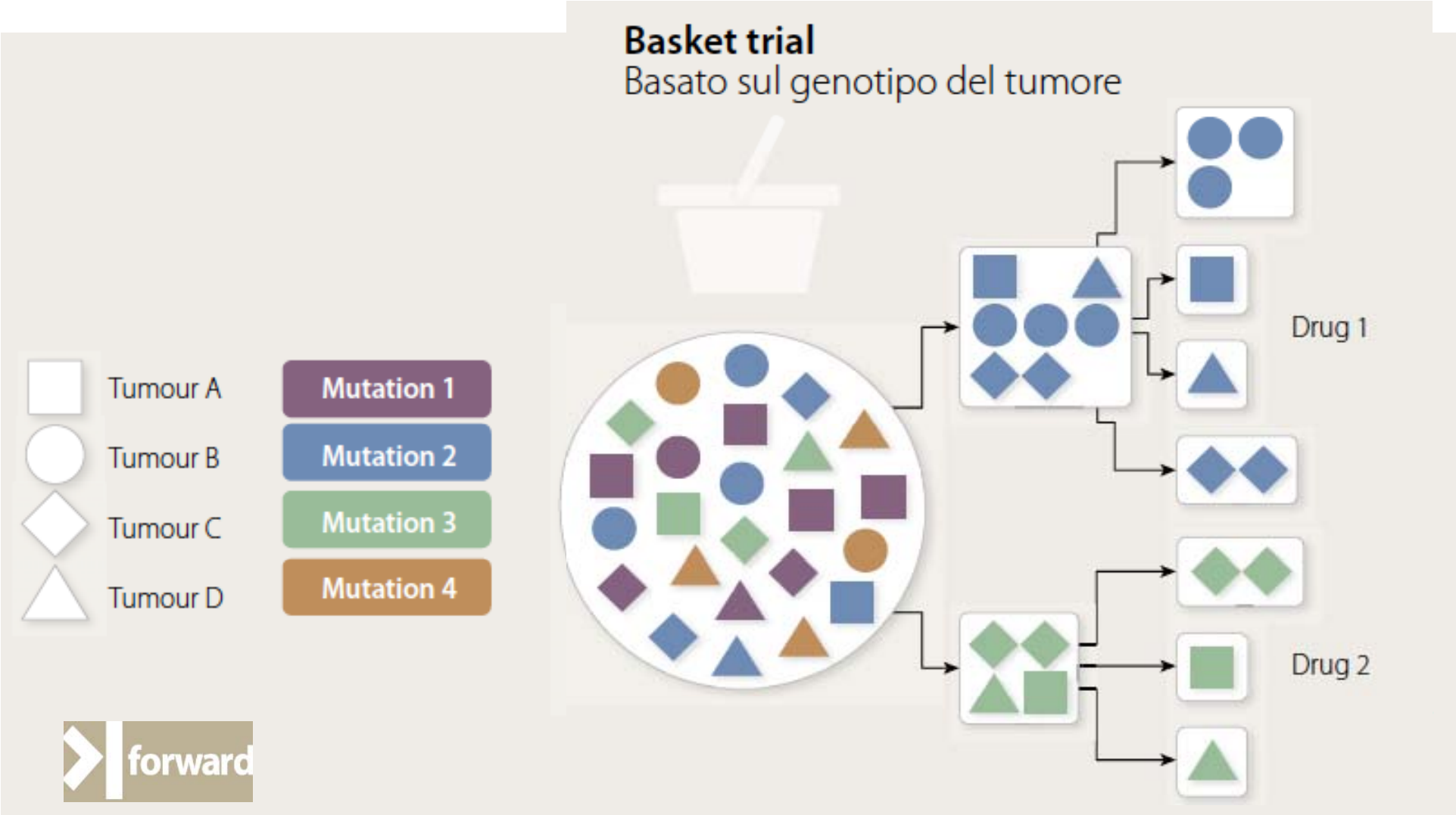


Source: Journal of Thoracic Oncology. 2014; 9(3):295-306

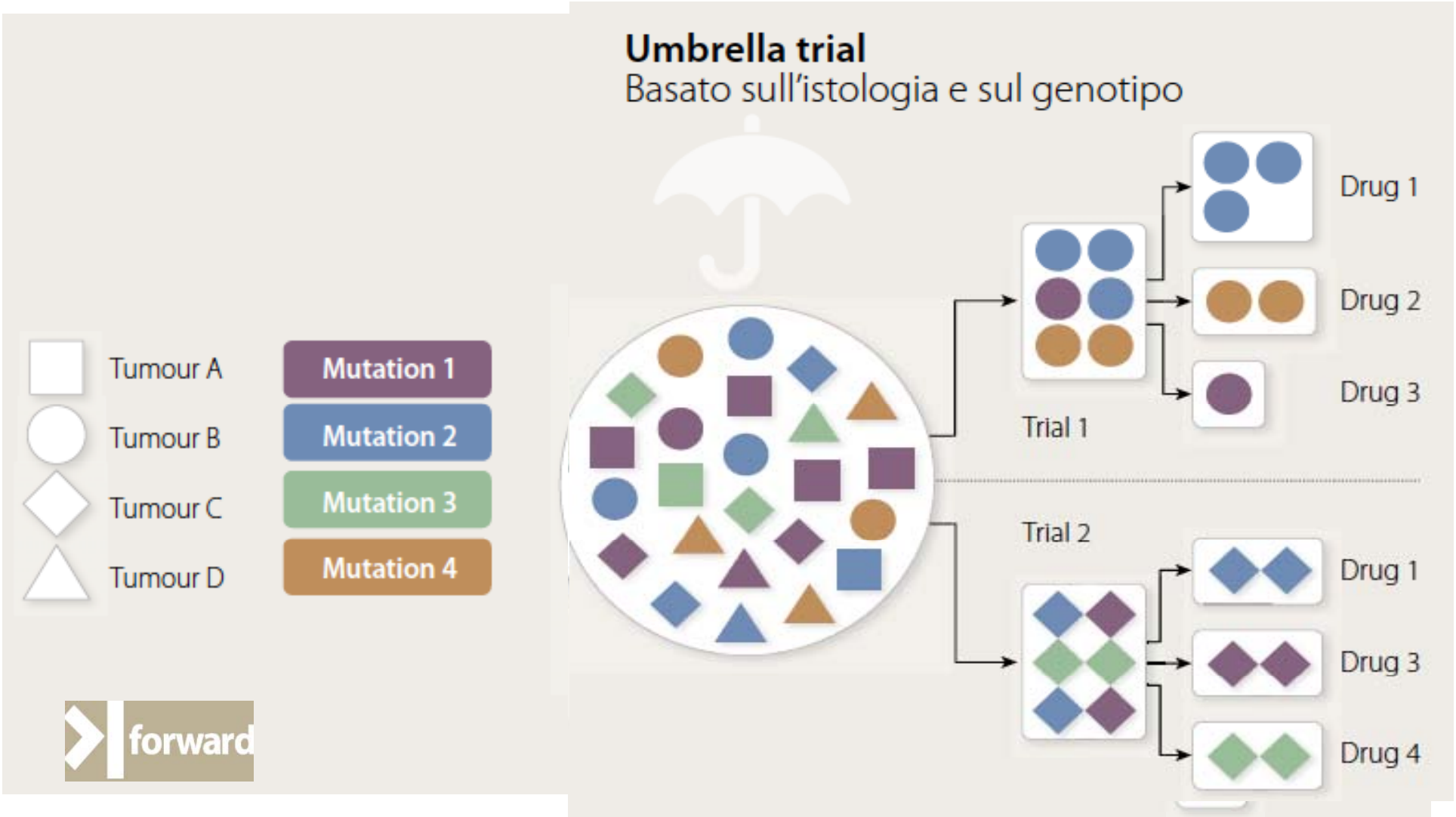
Una Nuova Metodologia di ricerca ?



Una Nuova Metodologia di ricerca ?



Una Nuova Metodologia di ricerca ?



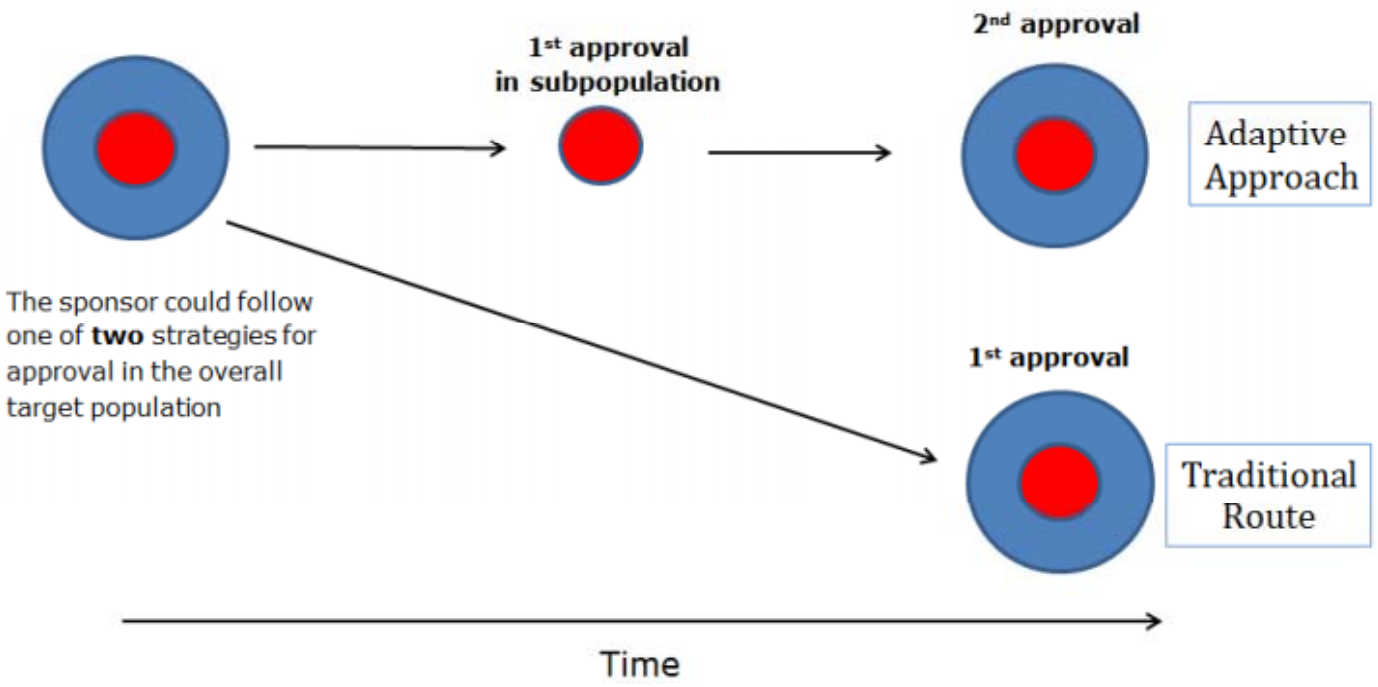
15 December 2014
EMA/758619/2014

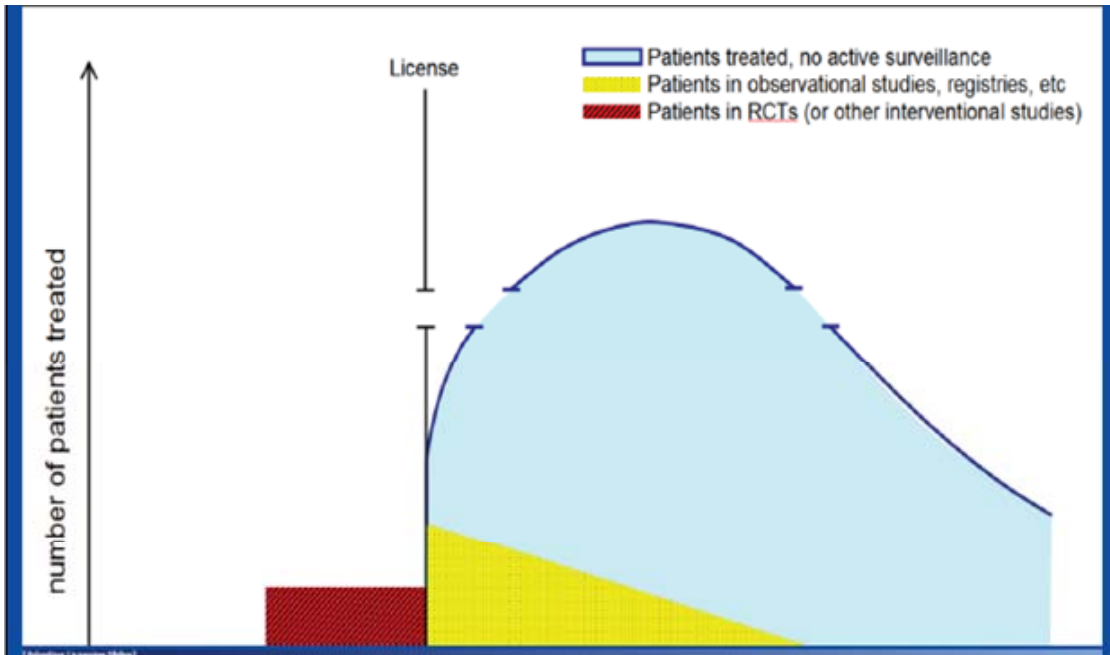
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

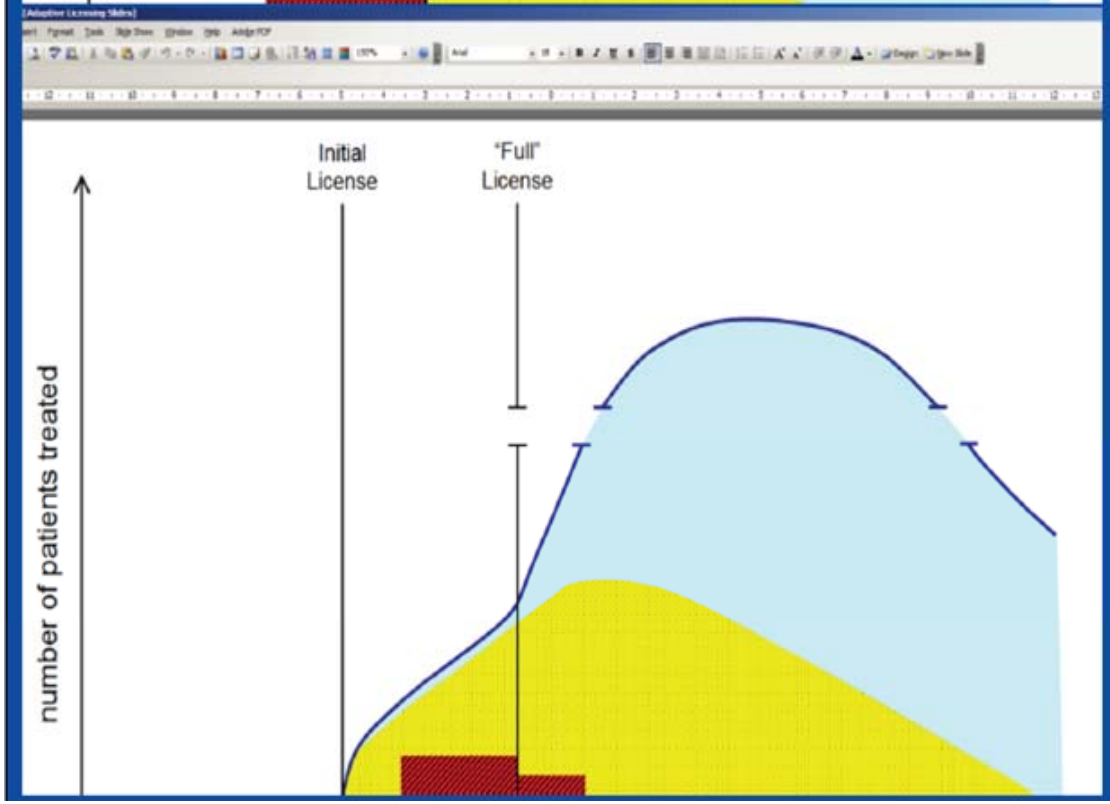
Adaptive pathways to patients: report on the initial experience of the pilot project

Widening of the indication Scenario

(Final target indication in blue and red)







Current scenario:

Post-licensing, treatment population grows rapidly; treatment experience does not contribute to evidence generation

Adaptive Licensing:

after initial license, number of treated patients grows more slowly, due to restrictions; patient experience is captured to contribute to real-world information

Tratta da Presentazione L.Pani Dublino 2013
www.agenziafarmaco.it

Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says **Nicholas J. Schork**.

ILLUSTRATION BY GREG CLARKE

- *Trials for cancer drugs were 2.8 times more likely not to be randomised, 2.6 times more likely not to use a comparator (single arm), and 1.8 times more likely not to be blinded.*

thebmj

BMJ 2015;350:h2068 doi: 10.1136/bmj.h2068 (Published 23 April 2015)

EDITORIALS

Why do cancer drugs get such an easy ride?

Rushed approvals result in a poor deal for both patients and cancer research

Donald W Light *professor*[1], Joel Lexchin *professor*[2]

[1]School of Osteopathic Medicine, Rowan University, Cherry Hill, NJ 08002, USA; [2]School of Health Policy and Management, York University, Toronto, ON, Canada

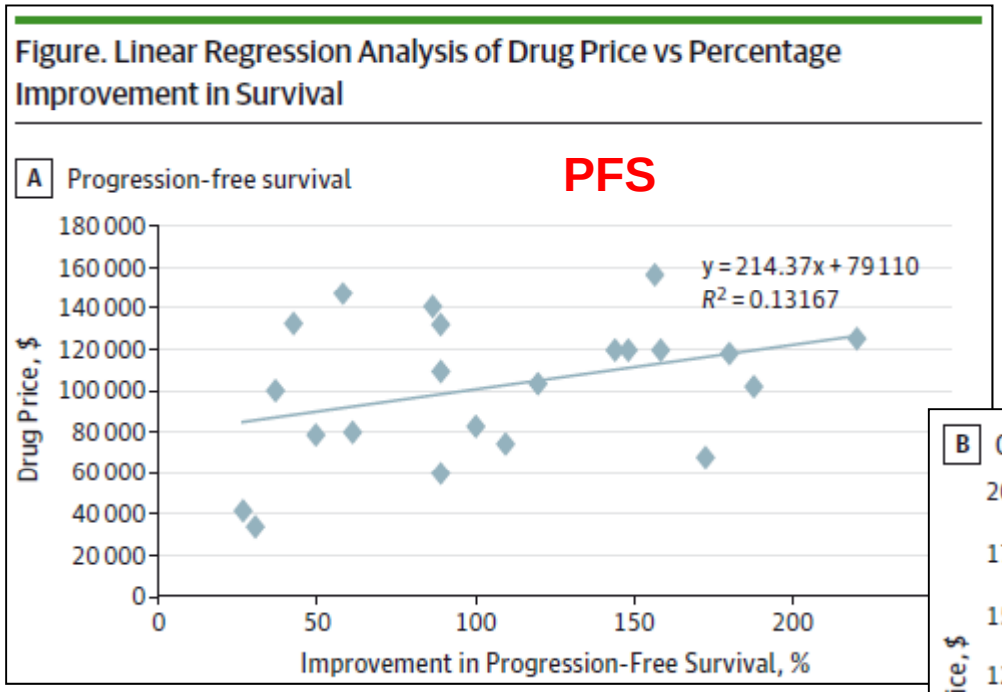
- *A review of drugs for solid cancers approved by the European Medicines Agency (EMA) in its first 10 years found that, overall, new oncology drugs improved survival by a mean and median of 1.5 and 1.2 months, respectively.*

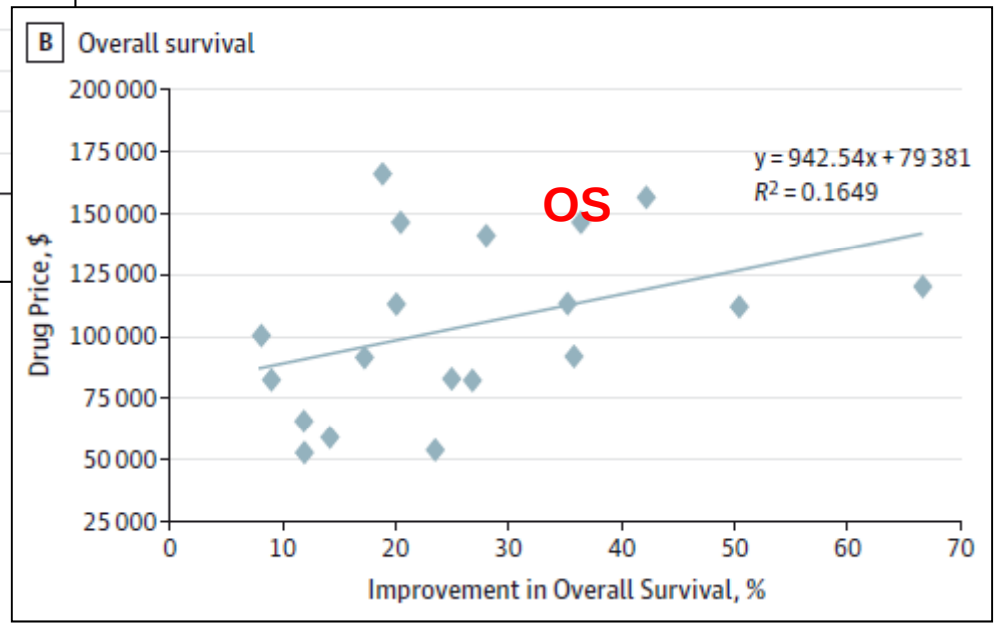
- *The 71 drugs approved by the FDA from 2002 to 2014 for solid tumours have resulted in median gains in progression-free and overall survival of only 2.5 and 2.1 months, respectively.*

- *In Europe between 1999 and 2009, oncology drugs were the class that was most likely to be approved through an accelerated pathway.*

- *In 2013, over 100 oncologists protested against the high prices charged for cancer drugs, when 11 out of 12 approved in 2012 provided only small benefits to patients*

Five Years of Cancer Drug Approvals:
Innovation, Efficacy, and Costs
*(*Mailankody & Prasad, *Jama oncology 2015)*





Come si sta attrezzando il settore regolatorio?

FIGURE 5: POLICY AND GUIDANCE DOCUMENTS FROM THE FDA

2005	Guidance on PG Data Submissions Concept Paper on Drug-Diagnostic Co-Development
2007	Guidance on Pharmacogenomic Tests and Genetic Tests for Heritable Markers
2008	E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories
2010	Guidance on Qualification Process for Drug Development Tools
2011	E16 Guidance on Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions
	Guidance on in vitro Companion Diagnostic Devices
2012	Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies
	Guidance on Clinical Trial Designs Employing Enrichment Designs
2013	Guidance on Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling
In Process	Guidance on Drug-Diagnostic Co-development

Source: Policy and guidance documents from the FDA.[72]

Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type *EGFR* tumours (TAILOR): a randomised controlled trial

Marina Chiara Garassino, Olga Martelli, Massimo Broggini, Gabriella Farina, Silvio Veronese, Eliana Rulli, Filippo Bianchi, Anna Bettini, Flavia Longo, Luca Moscetti, Maurizio Tomirotti, Mirko Marabese, Monica Ganzinelli, Calogero Lauricella, Roberto Labianca, Irene Floriani, Giuseppe Giaccone, Valter Torri, Alberto Scanni, Silvia Marsoni, on behalf of the TAILOR trialists

Summary

Background Erlotinib is registered for treatment of all patients with advanced non-small-cell lung cancer (NSCLC). However, its efficacy for treatment of patients whose tumours are *EGFR* wild-type—which includes most patients—is still contentious. We assessed the efficacy of erlotinib compared with a standard second-line chemotherapy in such patients.

Methods We did this randomised controlled trial in 52 Italian hospitals. We enrolled patients who had metastatic NSCLC, had had platinum-based chemotherapy, and had wild-type *EGFR* as assessed by direct sequencing. Patients were randomly assigned centrally (1:1) to receive either erlotinib orally 150 mg/day or docetaxel intravenously 75 mg/m² every 21 days or 35 mg/m² on days 1, 8, and 15, every 28 days. Randomisation was stratified by centre, stage, type of first-line chemotherapy, and performance status. Patients and investigators who gave treatments or assessed outcomes were not masked to treatment allocation, investigators who analysed results were. The primary endpoint was overall survival in the intention-to-treat population. The study is registered at ClinicalTrials.gov, number NCT00637910.

Findings We screened 702 patients, of whom we genotyped 540. 222 patients were enrolled (110 assigned to docetaxel *vs* 112 assigned to erlotinib). Median overall survival was 8·2 months (95% CI 5·8–10·9) with docetaxel versus 5·4 months (4·5–6·8) with erlotinib (adjusted hazard ratio [HR] 0·73, 95% CI 0·53–1·00; p=0·05). Progression-free survival was significantly better with docetaxel than with erlotinib: median progression-free survival was 2·9 months (95% CI 2·4–3·8) with docetaxel versus 2·4 months (2·1–2·6) with erlotinib (adjusted HR 0·71, 95% CI 0·53–0·95; p=0·02). The most common grade 3–4 toxic effects were: low absolute neutrophil count (21 [20%] of 104 in the docetaxel group *vs* none of 107 in the erlotinib group), skin toxic effects (none *vs* 15 [14%]), and asthenia (ten [10%] *vs* six [6%]).

Interpretation Our results show that chemotherapy is more effective than erlotinib for second-line treatment for previously treated patients with NSCLC who have wild-type *EGFR* tumours.

Funding Agenzia Italiana del Farmaco.

Lancet Oncol 2013; 14: 981–88

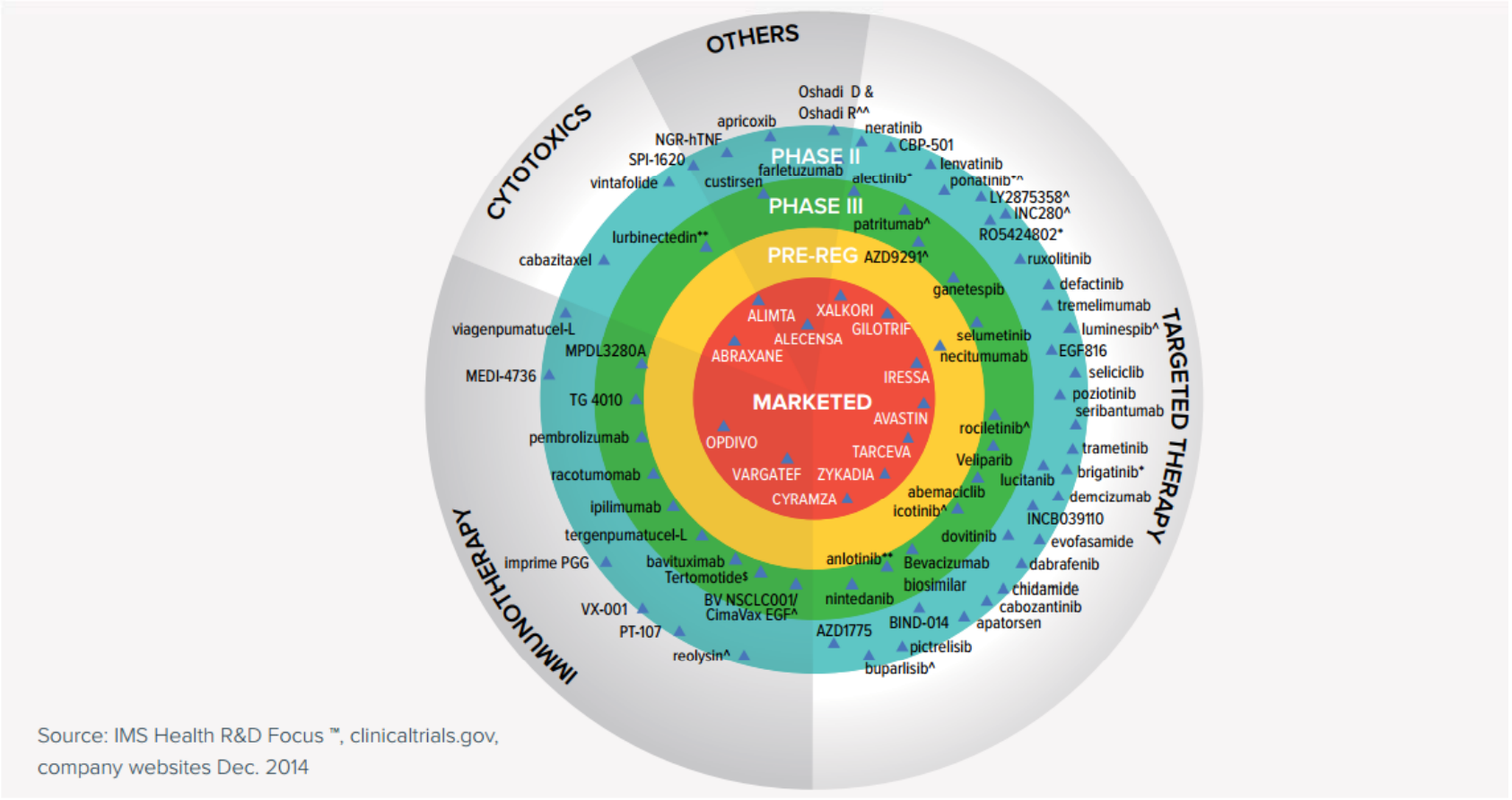
Published Online July 22, 2013 http://dx.doi.org/10.1016/S1470-2045(13)70310-3

See Comment page 916

Department of Medical Oncology (M C Garassino MD, G Farina MD, A Scanni MD), **Department of Pathology** (F Bianchi MD, M Ganzinelli PhD) **Fatebenefratelli e Oftalmico Hospital, Milan, Italy; Department of Medical Oncology, San Giovanni e Addolorata Hospital, Rome, Italy** (O Martelli MD); **Department of Oncology, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy** (M Broggini PhD, E Rulli PhD, M Marabese PhD, I Floriani PhD, V Torri MD); **Department of Laboratory Medicine, Niguarda Cà Granda Hospital, Milan, Italy** (S Veronese PhD, C Lauricella PhD); **Department of Medical Oncology, PapaGiovanni XXIII Hospital,**

Cosa ci dobbiamo aspettare

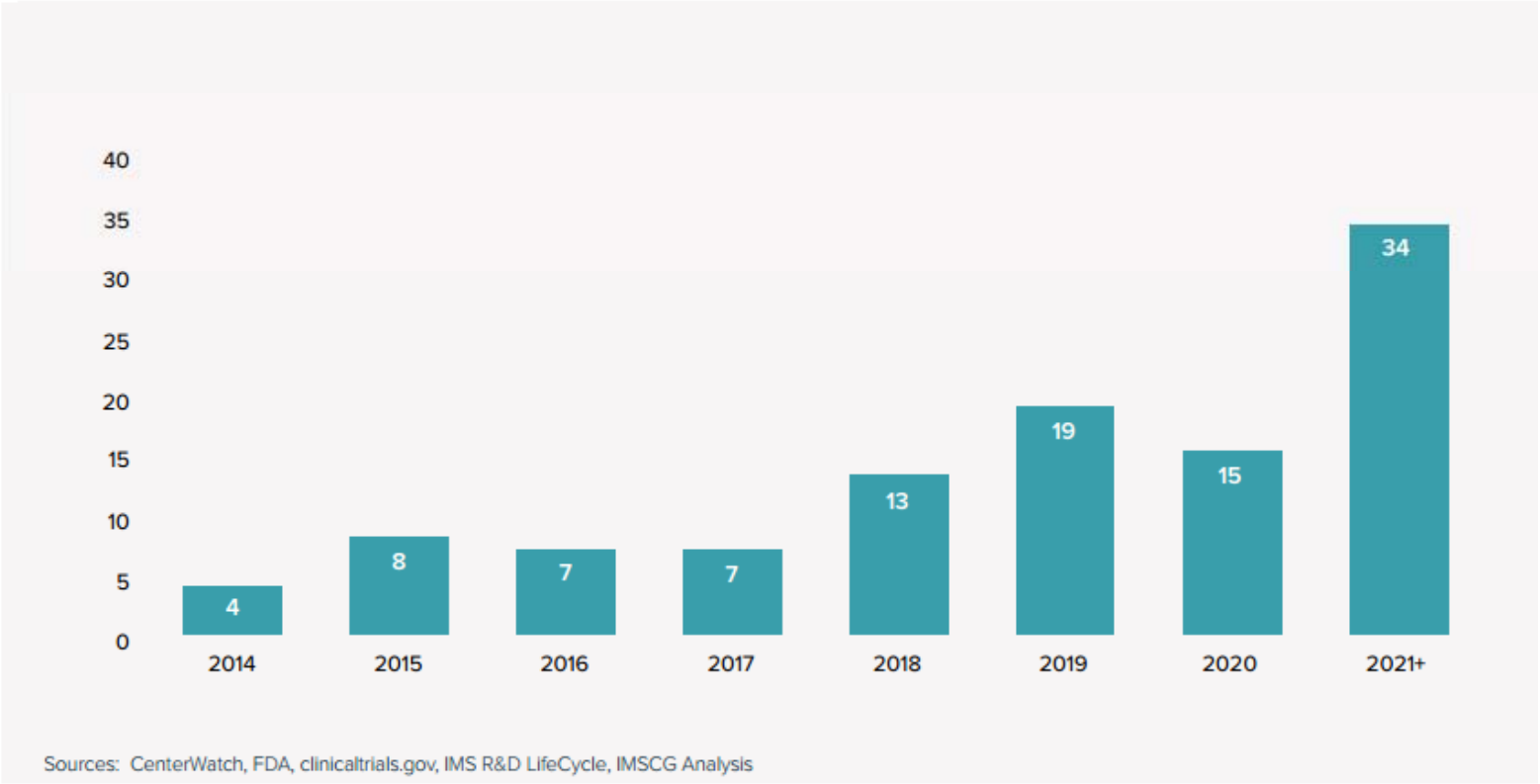
Key In-Market and Investigational Agents for NSCLC



Source: IMS Health R&D Focus ™, clinicaltrials.gov, company websites Dec. 2014

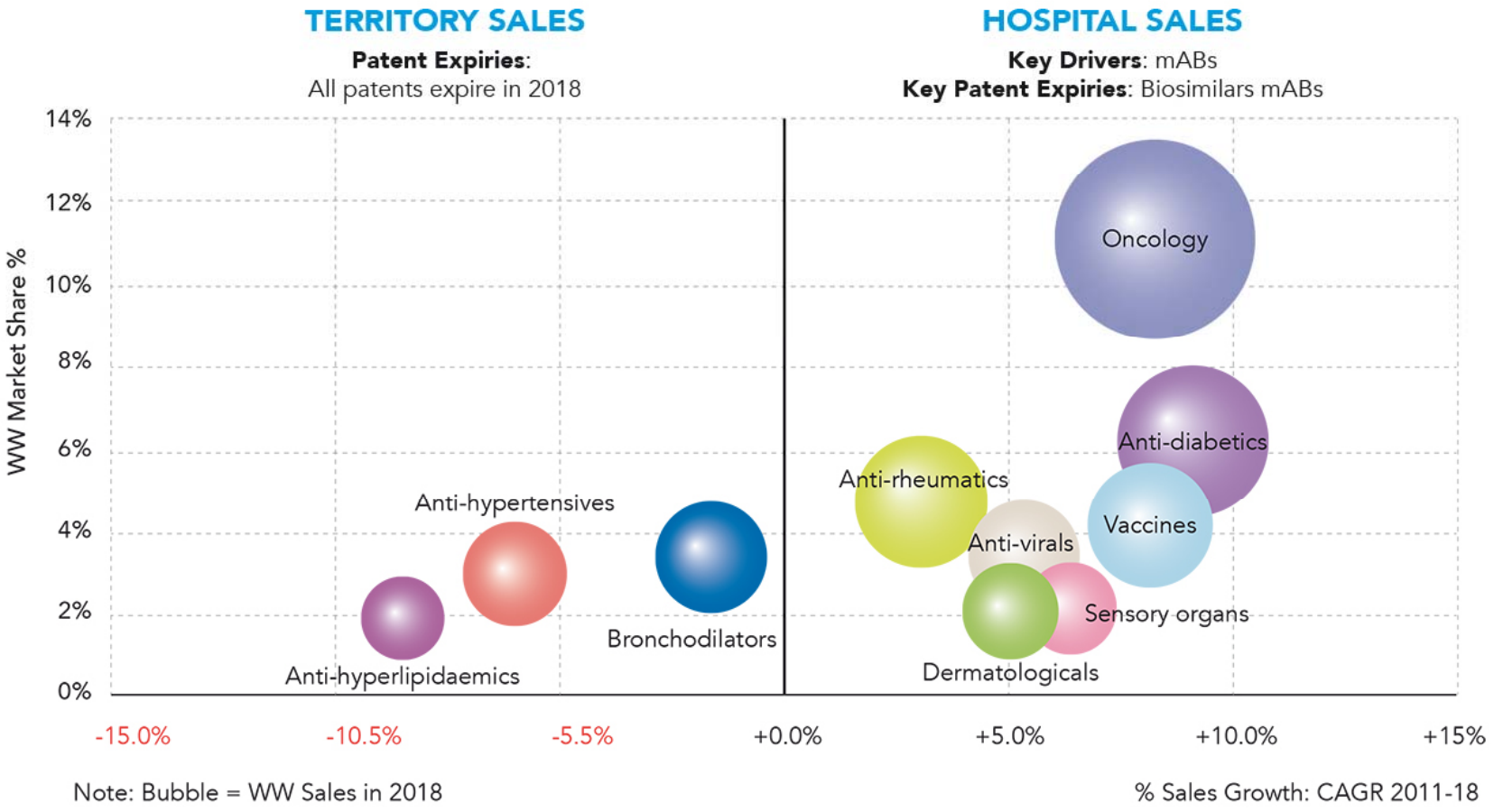
Over the next 5+ years, combinations of targeted and immuno-oncology agents will account for many NME launches and line extensions

Expected Combination Regimen Launches in Oncology



Sources: CenterWatch, FDA, clinicaltrials.gov, IMS R&D LifeCycle, IMSCG Analysis

Forecasting delle prime 10 categorie terapeutiche 2011- 2018



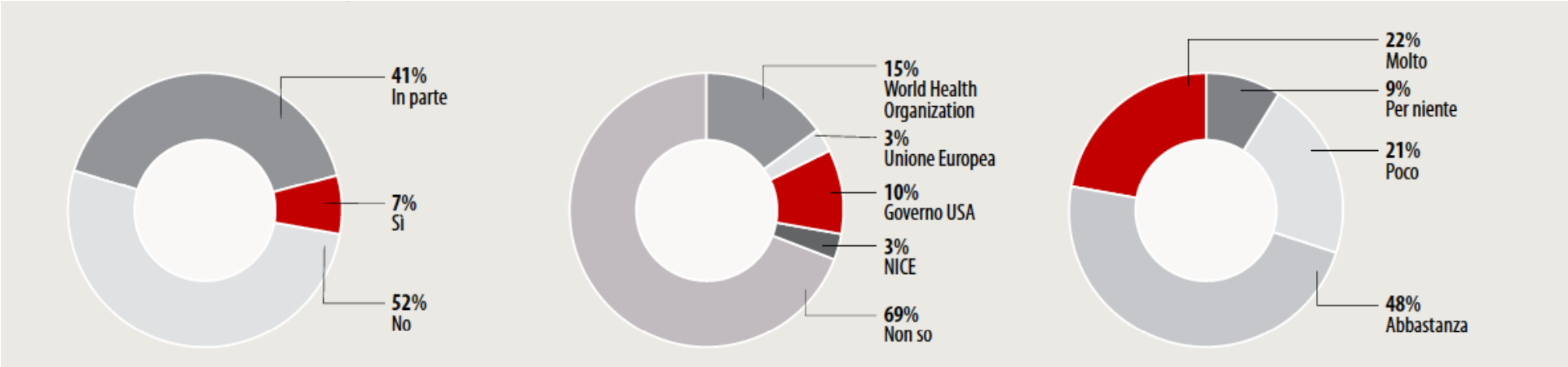
ASCO 2015 - Regiment Cost

80 Kg patient

Regiment	Cost of nivolumab	Cost of ipilimumab	Cost of Regimen
Nivo + Ipi for 11.5 m	$ 144.408	$ 151.158	$ 295.566

Medicina di precisione: un'indagine sui professionisti sanitari

forward

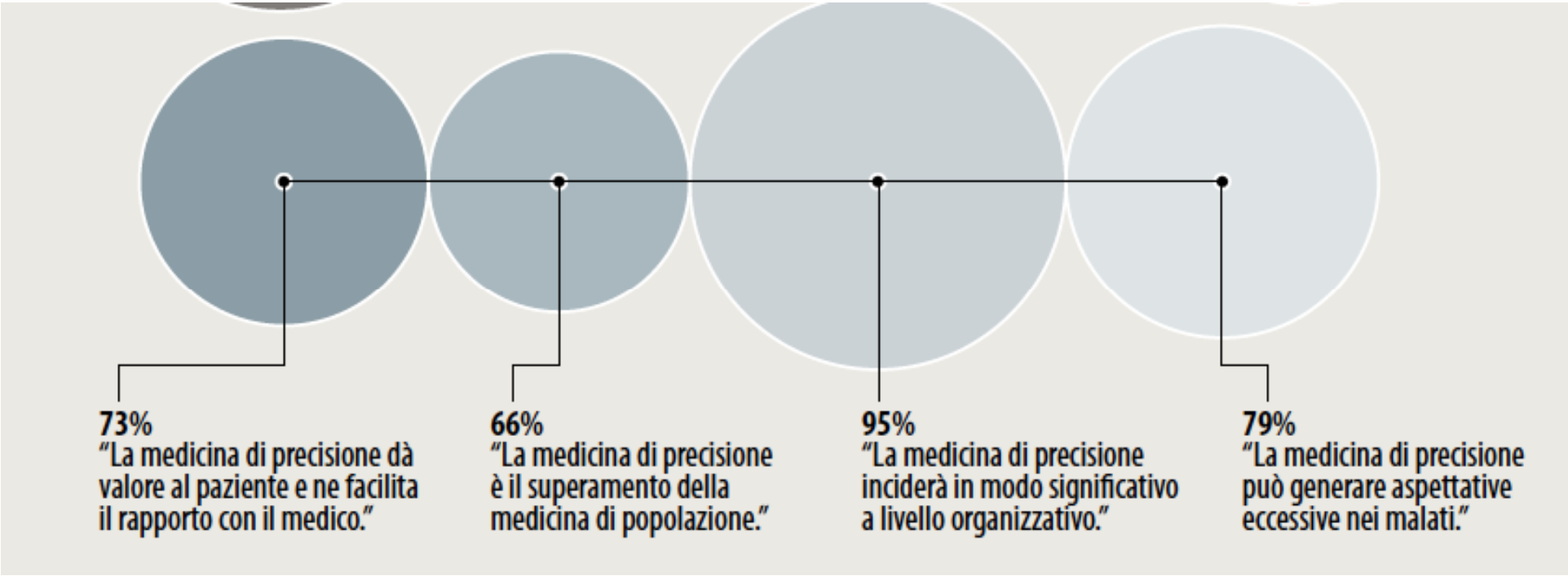


Sa di cosa si tratta?

Chi ha lanciato l'iniziativa?

MdP e MI sono sinonimi?

Medicina di precisione: un'indagine sui professionisti sanitari



forward

Council of the European Union

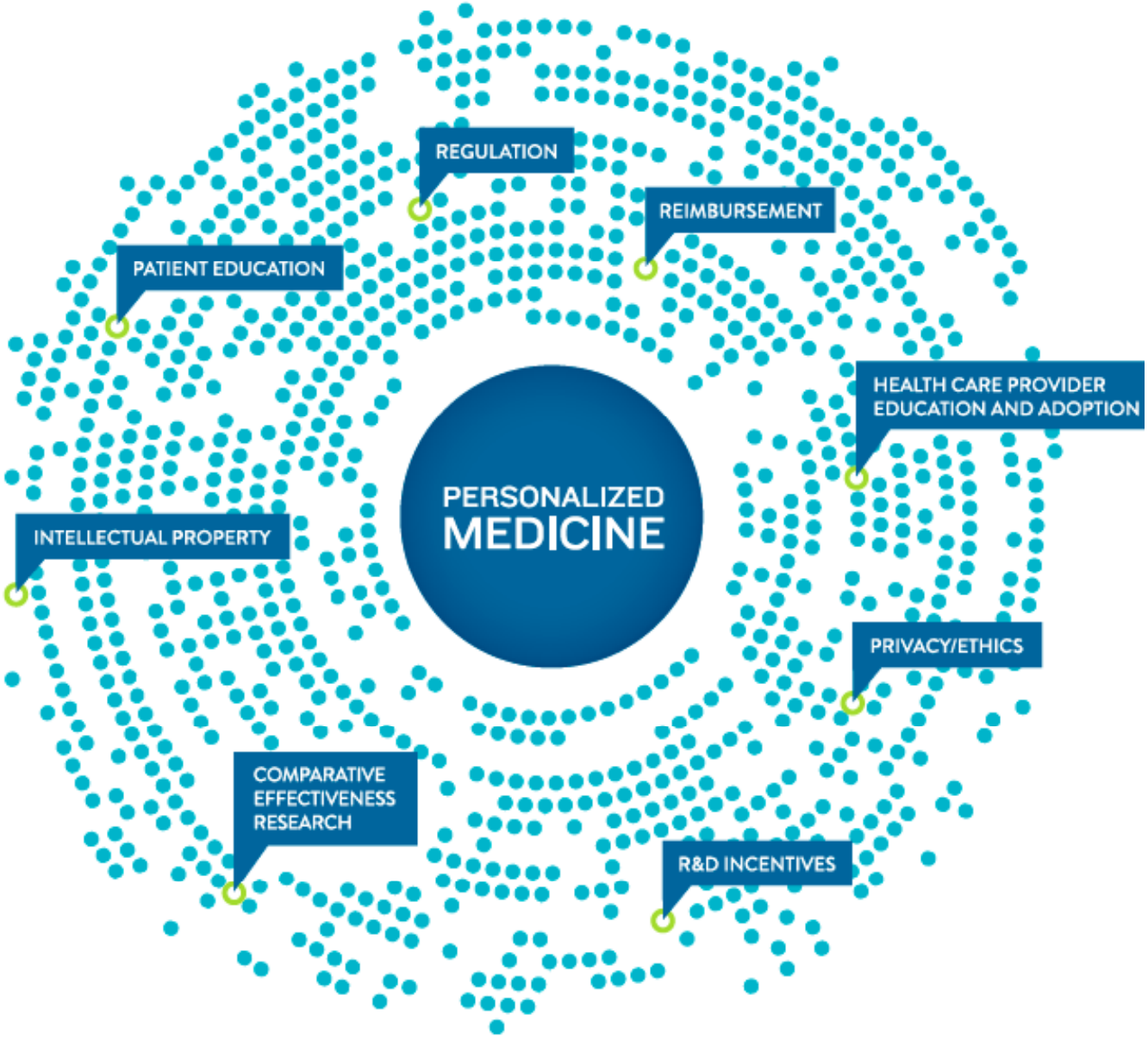
Brussels, 26 November 2015
(OR. en)

14393/15

NOTE

From:	General Secretariat of the Council
To:	Permanent Representatives Committee/Council
Subject:	**Employment, Social Policy, Health and Consumer Affairs Council** meeting on 7 December 2015 Draft Council conclusions on Personalised medicine for patients - Adoption (Public debate in accordance with Article 8(2) of the Council's Rules of Procedure [proposed by the Presidency])

The implementation of personalized medicine requires a confluence of multiple factors. Full implementation of personalized medicine can only be achieved when all sectors converge toward the center.




COME VEDETE QUESTO NUOVO FARMACO E' RISULTATO ESTREMAMENTE EFFICACE...PURTROPPO NON SAPPIAMO ANCORA SU COSA...
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