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Special Symposium:
The impact on health services from personalised targeted therapies
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Personalised Medicine in National Cancer Plans: How can innovation be translated into policy?

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This presentation

- National Cancer Control Programmes (NCCPs): a policy framework for cancer control
- Personalised or precision medicine within NCCPs
- Health system implications
  - Validated diagnostic tests
  - Drug development
  - Infrastructures and technology
  - Regulatory issues
  - Financing personalised medicine
  - Training for health professionals
- Preparing for the future: integrating PM concepts into current National Cancer Plans

Pillars of cancer care

European Guide for Quality National Cancer Control Programmes (developed within EPAAC working group on NCCPs)

- **Cancer prevention**
  - Primary prevention
  - Secondary prevention
- **Integrated care**
  - Diagnosis and treatment
  - Psychosocial care
  - Survivorship and rehabilitation
  - Palliative and end-of-life care
- **Supportive functions within the health system**
  - Governance and financing
  - Cancer resources
  - Cancer data and information
  - Research

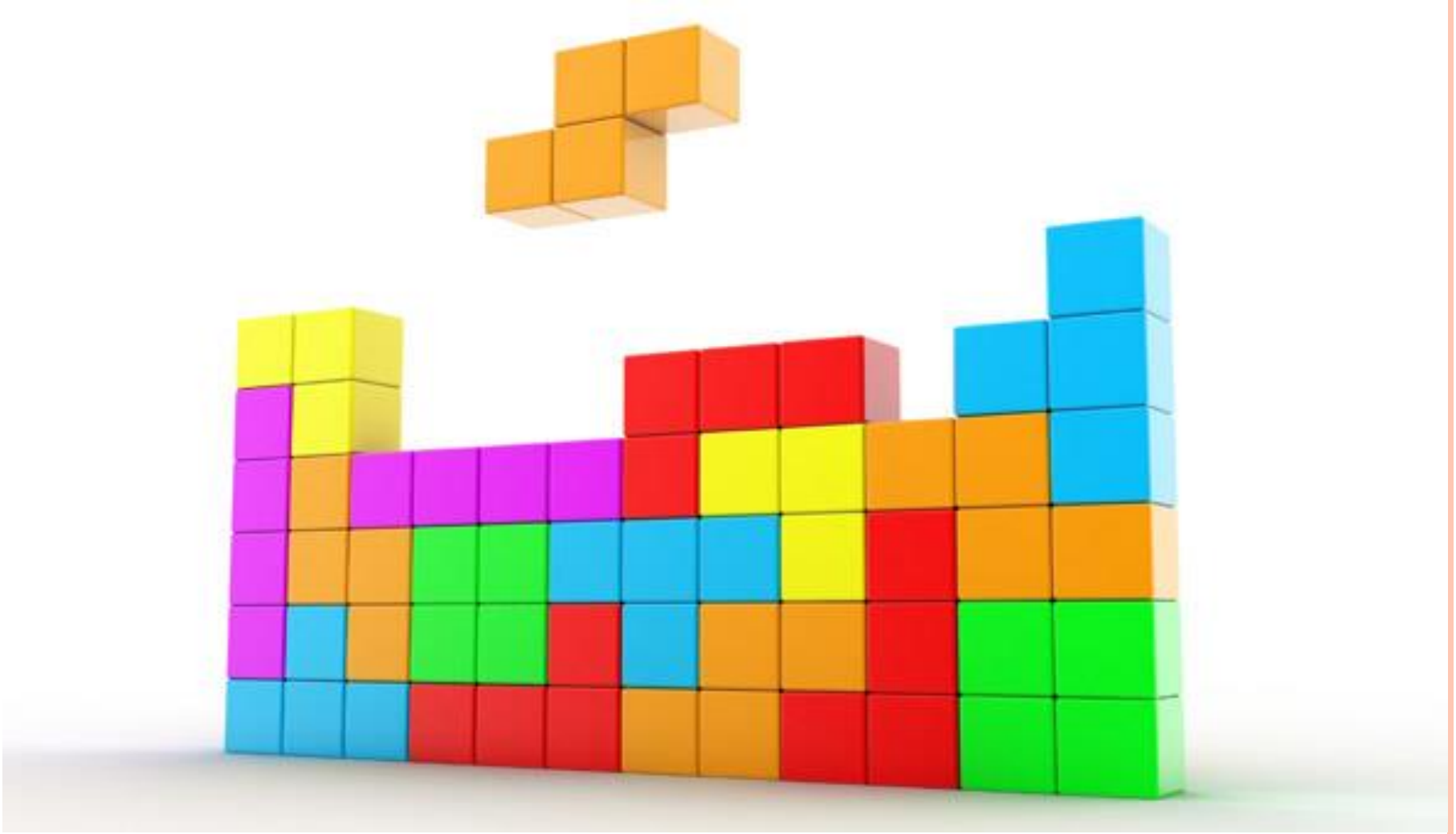
NCCPs in Europe

- Most Member States now use NCCPs as a policy framework to organise cancer prevention and care.
- Goals include:
  - Optimising resource use
  - Articulating different components of the health system to work together
  - Promoting a patient-based care model

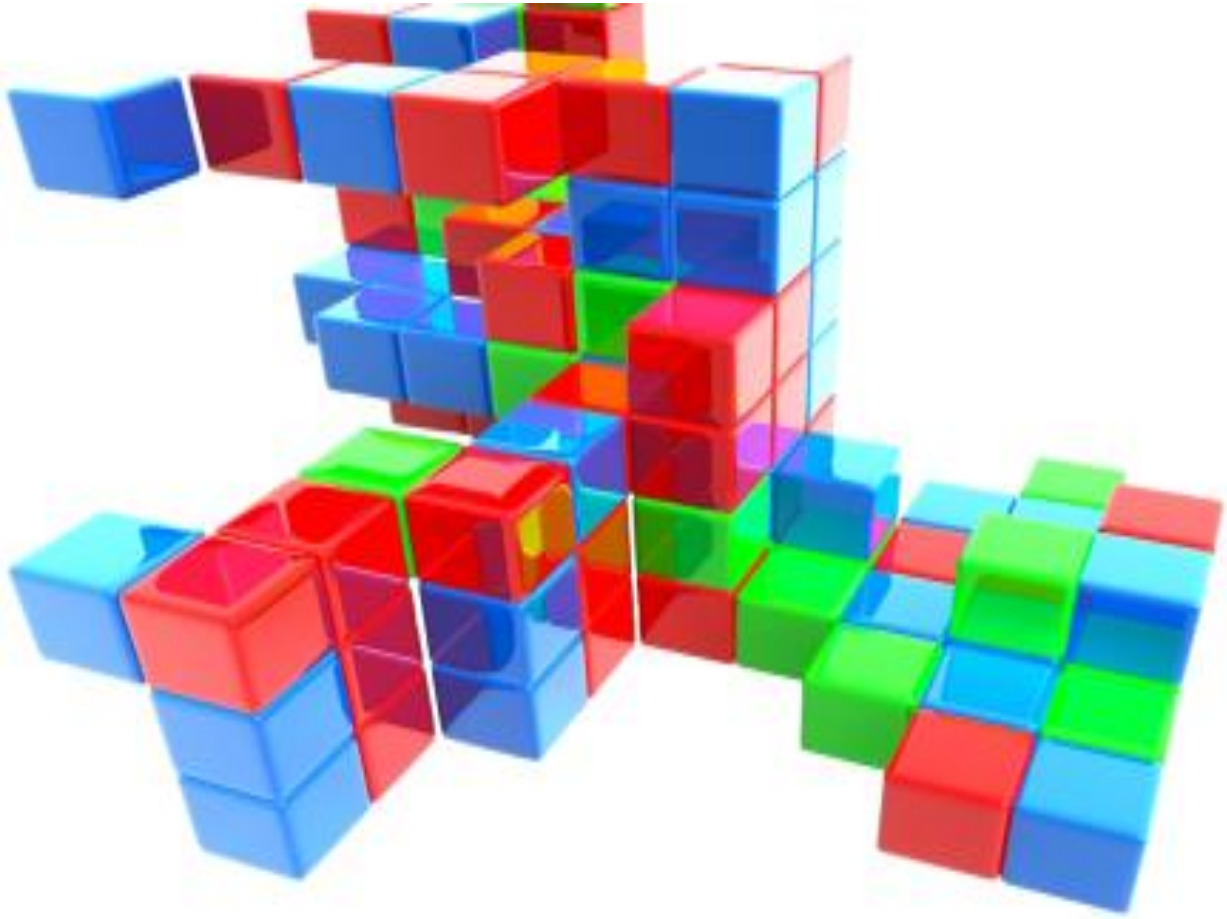
What does innovation mean for NCCPs?
Going back to the basics, before introducing innovations

- NCCPs often set out medium- to long-term road maps for cancer control at a national level
  - Funding and resources are allocated
  - HR training plans implemented
  - Information systems established or upgraded
  - Research grants awarded
  - Regulatory framework aligned with NCCP requirements and goals
  - Accountability dimension . . .

And then, when all the pieces start to fall into place . . .



Innovation changes the game



What benefits can PM bring to prevention, diagnosis and treatment?

- Diagnostic screening for disease risk and early detection
- New definitions of patient populations and disease targets
- Less “trial and error” and more tailored treatments

ESMO Position Paper

editorials

Annals of Oncology 25: 1673–1678, 2014
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Delivering precision medicine in oncology today and in future—the promise and challenges of personalised cancer medicine: a position paper by the European Society for Medical Oncology (ESMO)

defining personalised cancer medicine

In its broadest sense, 'personalised medicine' is the tailoring of medical treatment to the characteristics of an individual patient and moves beyond the current approach of stratifying patients into treatment groups based on phenotypic biomarkers. Nowhere in medicine has the impact of personalised medicine been greater than in oncology. For scientists and oncologists, the term 'personalised medicine' is often used interchangeably with terms such as 'genomic medicine', 'precision medicine' and 'precision oncology'. These terms are used to describe the use of an individual patient's molecular information (including genomics and proteomics) to inform diagnosis, prognosis, treatment and prevention of cancer for that patient. As the transition from stratified cancer medicine to truly personalised cancer medicine intensifies, it is this definition that the ESMO Personalised Medicine Task Force prefers to use when describing personalised cancer medicine. But irrespective of the term used, the direction of travel is clear—precision diagnosis and treatment of cancer at the molecular level—and this change in paradigm has profound implications, from preclinical definition of mechanism of action to the development of molecular taxonomies of cancer, and from genome diagnostics to trial design.

from genomics to clinics—the context and history of personalised medicine

Although much of cancer biology is based on the central tenet that it is a genetic disease, caused by a clone of cells that expands in an unregulated fashion because of somatically acquired mutations, this view contributed little to cancer treatment until the 21st century. The targeting of *HER2* overexpression with the monoclonal antibody, trastuzumab, to improve outcome in metastatic breast cancer was the first example of targeted treatment [1]; but the paradigm of targeted interference of an oncogene with a specifically designed small molecular inhibitor is best exemplified by imatinib. The tyrosine kinase inhibitor imatinib, developed to target the *BCR-ABL* fusion gene, a consequence of the Philadelphia chromosome and pathognomonic of chronic myeloid leukaemia, transformed the care of patients, changing this aggressive, life-threatening disease to a manageable chronic disease [2]. Around the same time, the initiation of the Cancer Genome Project at the Wellcome Trust's Sanger Institute using exon Sanger sequencing quickly identified somatic mutations in the *BRAF* gene in the majority of malignant melanoma [3]. This opened a window into the biology of these tumours and provided the starting point for successful clinical translation, with the development of vemurafenib that specifically targets the underlying molecular lesion [4].

With the launch of large-scale cancer whole genome sequencing (WGS) projects such as the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA) expected to deliver a complete catalogue of genomic alterations in primary cancers and begin to elucidate the mutational patterns and influences across the natural history of cancers [5, 6], connecting recurrent genomic alterations to altered pathways and acquired cellular vulnerabilities will open the door to targeted therapies [6]. At the same time, elucidation of the mechanisms underlying the processes generating somatic mutations will lead to new insights into cancer causation and, potentially, new approaches to prevention [7].

oncology—at the frontline of utilising personalised medicine

Oncology is at the frontline of personalised medicine, moving beyond the previous model of giving cancer therapeutics based on trials of largely unselected patients beyond a simple phenotypic marker, to leading the way in utilising the molecular profile of an individual's cancer genome to optimise their disease management. At the centre is the patient, with personalised medicine offering the promise of delivering safe and efficacious cancer treatments that are targeted, biologically rational and avoid over- and under-treatment common with traditional chemotherapy, thus reducing toxicities associated with non-specific modes of action of chemotherapy. An intriguing example is the characterisation of germline variations in cancer patients that predict anthracycline-related cardiomyopathy and cisplatin-associated ototoxicity and now provide a mechanism for prospective identification of at-risk patients [8, 9].

The experiences of the oncology community in developing and delivering precision medicine are not unique and have parallels, more broadly, in other areas of medicine. For example the progress made in cystic fibrosis (CF) in developing treatments to correct the basic CF transmembrane conductance regulator protein has profoundly changed CF in a way that closely mirrors oncology, in particular the development of the novel drug, ivacaftor for molecularly distinct sub-types of CF when the mutational class is confirmed by companion diagnostic testing [10]. In addition, genomic sequencing is transforming the diagnosis

What about implications for the rest of the health system?

Implementing PM will require integration into every corner of the health system, from basic medical research to specialised care, and everything in between:

- Drug development
- Technologies and infrastructure
- Regulatory issues for drugs and diagnostics
- Financing and resource allocation
- Professional training

1. Validated Diagnostic Tests + Drug Development

- Research into biomarkers using -omics
- Development of "blockbuster" drugs, with randomised clinical trials, may become obsolete in some cases
- New assessment routines, indicators and technologies must be developed
- Agreements and collaboration between industry and regulatory agencies are necessary

Necessary changes to drug development

USA-based Cancer Biomarkers Collaborative (CBC) Cancer Biomarkers Collaborative (CBC) proposed some solutions in 2010*:

- Development and agreement on quality standards for biomarkers and routines for quality assessment
- Harmonisation of biomarker validation
- Collaboration between drug developers and regulatory agencies
- Agreement on best practices for co-development of diagnostics and drugs
- Educating citizens and health professionals on the need to collect biomarkers

**Khleif SN, et al., Clinical Cancer Research, July 2010*

2. Infrastructure and technology

- Bringing –omics technologies from biomarker research (including proper validation procedures) to clinical development settings
- Increasing access to imaging technologies (MRI, PET, CIT)
- Development and maintenance of data and biobanks capable of storing large amounts of patient information

Issues to resolve:

- Equitable distribution of investment burden among researchers, institutions, payers and hospitals, to store and access patient data
- Ethical issues on exchange and use of patient data

3A. Regulatory issues: drugs

- For **drugs**, changes to regulatory structures will likely be minimal:
  - PM will narrow the target patient population, but drugs will still go through a centralised process through the European Medicines Agency (EMA), according to well-established quality and safety standards
  - PM drugs will simply need to be approved in conjunction with a companion diagnostic

3B. Regulatory issues: Diagnostics

Regulations surrounding diagnostics are not as straightforward:

- Diagnostics are currently handled at national level with only basic EU regulation, not through the EMA
- No present requirement to coordinate the clinical validation of a diagnostic test with its companion drug

In practice, this means that we have to address this challenge in order to effectively regulate the PM approach (which depends on the combination of precision drugs with diagnostic tests to *personalise* patient treatment) at an EU level and in Member States.

4. Financing Personalised Medicine

- PM advocates argue that better diagnostics, combined with precision therapies, will allow us to use resources more efficiently and provide better patient care
- Yet, implementing the complex systems required for a PM approach require considerable investments up front, raising concerns about equity and access
- Health Technology Assessments will also have to become more complex, taking into consideration the inputs as well as the costs saved by averting other clinical interventions.

5. Professional training

- Need to incorporate training in IT and clinical genetics into MD and nursing programmes, so that professionals can recognise indicators of genetic risk and understand how to process data
- Continuing education will have to keep up with a rapidly developing field
- Opening clinical research opportunities for practicing physicians

Are we ready to overhaul health systems to set the foundation for a PM approach?

- Although PM has enormous potential for the future, it is still premature to implement large-scale changes to cancer policy
- The benefits of the PM approach will not be immediately revolutionary, but incremental, with inevitable missteps and adjustments

TOWARDS MAKING THIS COMPATIBLE WITH EQUITY / UNIVERSAL HEALTH COVERAGE

DEFINITION OF COVERAGE

The probability of receiving a necessary health intervention conditional on the presence of a health care need

$$C_j = \frac{\sum_i C_{ij} d_{ij}}{\sum_i d_{ij}}$$

New definition of effective coverage

The magnitude of the realised health gain from the intervention relative to the potential health gain possible with the optimal performance of the providers for a given health system

$$EC_j = \frac{\sum_{i=1}^{n} HG_{ij} C_{ij} d_{ij}}{\sum_{i=1}^{n} (HG_{ij} \mid P_{jk} = P_{opt}, R_{jk} = 1, Y_{ij} = 1, \forall k = 1...) d_{ij}}$$

Source: slided extacted from presentation on UHC by Dr Michel Thieren (WHO/EIP/MHI)

PM is just one piece of cancer control

Personalised medicine can sometimes be portrayed as "the" answer to cancer control, but in fact, it is only one of many.

Keys to the rational integration of PM into NCCPs

- Assessing the current situation and the future prospects
- Anticipating needs and challenges
- Involving stakeholders
- Developing a multi-pronged strategy and roles for implementation
- Balancing PM potential with the proven efficacy of other cancer control strategies (tobacco control, screening, multidisciplinary care models, etc.)
- Creating mechanisms for evaluation, strategic adaptation and accountability
- Considering equity and access at a European level

"Every patient – regardless of where he or she is born – deserves an equal chance at a long life and good health"

(Seffrin, 2008)

Slide provided by Dr. Eduardo Cazap

GCTF ESMO &Latin American and Caribbean Society of Medical Oncology (SLACOM)

Conclusions

- PM is scientifically exciting, but its implementation requires systemic adjustments and important up-front investments
- Adjustments are needed to adapt drug and diagnostics development process, regulatory frameworks, technological and infrastructure resources, and human resources with an eye to future preparedness
- PM will become increasingly important, and now is the time to set the groundwork for its gradual implementation, always keeping in mind issues of equity, ethics and efficiency.

Thanks!

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