

SPECIAL ARTICLE

The European Society for Medical Oncology (ESMO) Precision Medicine Glossary

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Background: Precision medicine is rapidly evolving within the field of oncology and has brought many new concepts and terminologies that are often poorly defined when first introduced, which may subsequently lead to miscommunication within the oncology community. The European Society for Medical Oncology (ESMO) recognises these challenges and is committed to support the adoption of precision medicine in oncology. To add clarity to the language used by oncologists and basic scientists within the context of precision medicine, the ESMO Translational Research and Personalised Medicine Working Group has developed a standardised glossary of relevant terms.

Materials and methods: Relevant terms for inclusion in the glossary were identified via an ESMO member survey conducted in Autumn 2016, and by the ESMO Translational Research and Personalised Medicine Working Group members. Each term was defined by experts in the field, discussed and, if necessary, modified by the Working Group before reaching consensus approval. A literature search was carried out to determine which of the terms, 'precision medicine' and 'personalised medicine', is most appropriate to describe this field.

Results: A total of 43 terms are included in the glossary, grouped into five main themes—(i) mechanisms of decision, (ii) characteristics of molecular alterations, (iii) tumour characteristics, (iv) clinical trials and statistics and (v) new research tools. The glossary classes 'precision medicine' or 'personalised medicine' as technically interchangeable but the term 'precision medicine' is favoured as it more accurately reflects the highly precise nature of new technologies that permit base pair resolution dissection of cancer genomes and is less likely to be misinterpreted.

Conclusions: The ESMO Precision Medicine Glossary provides a resource to facilitate consistent communication in this field by clarifying and raising awareness of the language employed in cancer research and oncology practice. The glossary will be a dynamic entity, undergoing expansion and refinement over the coming years.

Key words: precision, personalised, oncology, glossary, translational

Introduction

'Precision medicine' or 'personalised medicine' is a rapidly evolving approach of tailoring therapeutic interventions to the individual molecular features of a patient and/or their disease that moves beyond the conventional approach of stratifying patients

into treatment groups based on phenotypic biomarkers. The European Society for Medical Oncology (ESMO) set out its ongoing commitment to support and shape the evolution of this paradigm shift in cancer treatment in a position paper published in 2015, recognising both the promise and challenges of this new

era of precision medicine to transform cancer care for patients, and the profound implications it has from preclinical definition of mechanism of action to the development of molecular taxonomies of cancer, and from genome diagnostics to trial design [1].

In oncology, central to precision medicine is the ability to characterise precisely the molecular and cellular features of a tumour, and its microenvironment, in addition to taking into account genetic markers, the life-style and environmental factors of the individual, to determine which treatments are likely to confer the greatest benefit [2]. Major scientific advances, in particular high-throughput sequencing technologies and animal models, therefore play a pivotal role in the translational research that underpins our current practice of medical oncology [3]. Over the last 5–10 years a large number of new terminologies to describe these concepts, have entered into the language of oncology specialists and cancer researchers. These terms, however, are frequently poorly defined when first introduced or are used interchangeably to either describe the same concept or mean different things when used by different authors and speakers. This relative lack of clarity can lead to confusion and miscommunication within the oncology community. Within its remit of improving patient care by supporting and promoting the accelerated adoption of high quality translational research and personalised medicine, the ESMO Translational Research and Personalised Medicine Working Group has developed a glossary to standardise the language used by oncologists within the context of precision medicine.

The 43 terms included in the glossary were identified by an ESMO member survey conducted in Autumn 2016, by ESMO Translational Research and Personalised Medicine Working Group members and by our reviewers. The terms included were those that were often misunderstood or felt to lack a clear definition. Each term was defined by experts in the field, discussed and, if necessary, modified by the Working Group before reaching consensus approval. Where terms are considered interchangeable this is specified. Dictionaries of scientific terms already exist, including the Glossary in Molecular Biology and The Glossary of Molecular Techniques that describe molecular processes and technical terminology relevant to translational research [4]. The current resource differs in that it focuses on the new concepts in precision medicine not covered in these existing glossaries. These concepts are grouped into five main themes—

(i) mechanisms of decision, (ii) characteristics of molecular alterations, (iii) tumour characteristics, (iv) clinical trials and statistics and (v) new research tools. The ultimate goal of the glossary is to facilitate clear communication between oncologists and basic scientists by clarifying and raising awareness of the language that we employ in cancer research and oncology practice. We envisage that the glossary will be a dynamic entity, undergoing expansion and refinement over the coming years.

Precision medicine is preferred to personalised medicine

During the creation of this glossary the concepts of ‘precision medicine’ and ‘personalised medicine’ generated the greatest discussion within the working group. We therefore take some time to explain why we have decided that the two terms are technically interchangeable but the term ‘precision medicine’ is favoured under the terms of the definition provided.

It is clear that current definition of ‘precision medicine’ is consistent with the earliest [5] and the most widely cited definitions of personalised medicine—‘the tailoring of medical treatment to the individual characteristics of each patient to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side-effects for those who will not’ [6]. A PubMed search of the cancer literature confirms that the term ‘personalised medicine’ predated that of ‘precision medicine’ and subsequently there has been a steep and continuous rise in the use of both terms, however, over the last 5 years the latter term has received much greater representation (Figure 1).

We have identified three reasons that may explain the preference for this newer term. The first was proposed by the National Research Council that suggested that the term ‘personalised’ could be ‘misinterpreted to imply that treatments and preventions are being developed uniquely for each individual’ [7]. A second reason is that many clinicians, including members of our working group, feel that the term ‘personalised medicine’ could describe all modern oncology practice that takes into account patient factors such as personal preference, cognitive aspects and co-morbidities in addition to treatment and disease factors. In this framework, personalised medicine is the holistic approach to

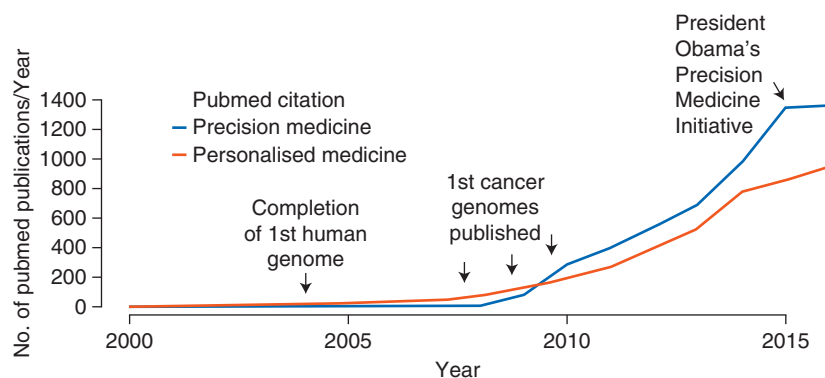


Figure 1. Number of PubMed publications per year including the terms ‘precision medicine AND cancer’ and ‘personalised medicine OR personalised medicine AND cancer’.

which biomarker based precision medicine is only one element. Thirdly, we feel that the term ‘precision medicine’ better reflects the highly accurate nature of new technologies that permit base pair resolution dissection of cancer genomes. Indeed, it is unlikely to be a coincidence that this new, possibly more aspirational and positive term, gathered popularity from 2009 onwards as the first human cancer genomes were published [8, 9] and clinical trials using targeted therapies, such as the EGFR inhibitor, gefitinib, in non-small-cell lung cancer and the BRAF kinase inhibitor, vemurafenib in melanoma, started to report some of the most encouraging advances in oncology in decades [10, 11].

Mechanisms of decision

Precision medicine (preferred term)/personalised medicine. A healthcare approach with the primary aim of identifying which interventions are likely to be of most benefit to which patients based upon the features of the individual and their disease. In cancer, the term usually refers to the use of therapeutics that are expected to confer benefit to a subset of patients whose cancer displays specific molecular or cellular features (most commonly genomic changes and gene or protein expression patterns). Nevertheless, the term also includes the use of prognostic markers, predictors of toxicities and any parameter such as environmental and lifestyle factors that leads to treatment tailoring. Characterisation approaches in the future are expected to encompass a wider range of technologies such as functional imaging.

Pharmacogenomics. A component of precision medicine—the study of how genomic variation within the individual or their disease (including gene expression, epigenetics, germline and somatic mutations) influences his/her response to drugs. In pharmacogenomics genomic variation is correlated with pharmacodynamics and pharmacokinetics. The aim of pharmacogenomics is to optimise drug therapy by maximising therapeutic effect and minimising adverse effects.

Stratified medicine. The use of a molecular assay to define subpopulations, rather than individuals, who are likely to benefit from a treatment intervention.

Molecular tumour board. A molecular tumour board is a specific type of multidisciplinary tumour board. In common with a classical multidisciplinary board it aims at providing clinical recommendations. A molecular tumour board, however, deals not only with the classical radiological, clinical and standard biological data of the patient, but also with modern molecular diagnostic tests. Its composition therefore goes beyond that of multidisciplinary boards, encompassing molecular biologists, geneticists and bioinformaticians.

Characteristics of molecular alterations

Mutation/genomic mutation. A permanent alteration in the DNA sequence that may be somatic (acquired during an individual’s lifetime) or germline (inherited). Alterations encompass point mutations, structural variants and copy number changes (all described below).

Cancer gene. Cancer genes are mutated forms of normal cell genes that through mutation can promote cancer development and progression. Cancer genes are broadly separated into oncogenes and tumour suppressor genes. Oncogenes promote cellular proliferation through either an increase in gene expression or through mutations that result in an increase in oncogene-encoded protein activity. In contrast, tumour suppressor genes act to oppose the processes that can drive cancer progression, such as cellular proliferation therefore, it is reduced expression or inactivation of the tumour suppressor gene protein product that contributes to carcinogenesis. By definition, cancer genes are under positive selection in a tumour and the statistical analysis of selection in genomic sequences from over 7000 cancers has identified around 200 cancer genes, but it is predicted that many more remain to be discovered [12].

Driver mutation. A genomic mutation that falls within a cancer gene (or its regulatory regions) and, by altering the cancer gene’s function or activity, provides a critical role in the development and/or maintenance of the tumour malignant phenotype, including cancer initiation, progression, maintenance or growth. An individual tumour may have several driver mutations. Recent estimates indicate that the average cancer has around 4 driver mutations but this varies between cancer types, ranging from one in thyroid and testicular cancers to more than 10 in endometrial and colorectal cancers [12].

Passenger mutation. A somatic mutation within either a coding or non-coding region of the genome that does not confer a selective growth advantage under a given set of selective pressures. Notably, this is an emerging field and some variants currently considered to be passenger mutations might be classified as driver mutations in the future when larger numbers of cancers are analysed or more functional data is available. Hundreds to thousands of passenger mutations are seen in most cancers and can reveal the processes underlying tumour aetiology and evolution. Passenger mutations are also seen in all normal cells and reflect exposure to intrinsic and extrinsic processes.

Oncogene addiction. Cancer cells harbour many genetic alterations and some of these occur in genes that are known to drive tumourigenesis (e.g. the BCR–ABL fusion gene in chronic myeloid leukaemia). The term oncogene addiction is used when a tumour becomes dependent on the expression and function of these driver genes and its ablation negatively impacts tumour maintenance and progression.

Pathogenic variant. A mutation that may be inherited (germline) or acquired (somatic) and predisposes an individual to a specific disease. Pathogenic variants may not be fully penetrant, i.e. the individual may not display the disease trait. For example, a female with a germline *BRCA1* mutation has an 80% risk of developing breast cancer in her lifetime.

Deleterious variant. In cancer this is used to describe a mutation that falls within a cancer gene and is predicted to inactivate or impair the encoded protein’s function.

Targetable genomic alteration/druggable genomic alteration. A genomic alteration that encodes an altered protein against which a drug exists or can be synthesised (for example, most kinases are targetable).

Actionable genomic alteration. Includes both targetable alterations and genomic alterations that cannot be directly targeted but that lead to dysregulation of a pathway in which there are possible targets (for example, alterations of the *PTEN* tumour suppressor gene can be targeted with PI3K/AKT inhibitors).

Point mutation. Focal mutations in genomic DNA including single or double nucleotide substitutions.

Insertion/deletion mutations. Insertions and deletions of (referred to as ‘indels’) that are typically small (1–5 bp) and less frequently medium, from 100 bp up to 30 kb or long (more than 30 kb). If the number of nucleotides in the insertion/deletion is not divisible by three, and occurs in a protein coding region, it is also named frameshift mutation.

Structural variant (preferred)/genomic rearrangement. Changes in the orientation, location or number of copies of segments of genomic DNA. Usually refers to DNA segments of ~1 kbp or larger and includes inversions, translocations, deletions and duplications.

Copy number variation (germline). Usually refers to germline copy number variants that contribute towards inter-individual genomic variability and may predispose to various inherited medical disorders. Copy number variation typically consists of deletions or variable number of copies of duplicated DNA segments that may contain as few as two to three nucleotides or entire genes.

Copy number alteration (somatic). Defines a change in copy number that has arisen in somatic cells including cancer cells. Encompasses gains and losses of chromosomal segments or whole chromosomes/chromosome arms in addition to high-level amplifications and focal deletions.

Gene amplification. A copy number increase of a restricted chromosomal region. Amplification is sometimes defined as a magnitude of gain that is more than twice the cancer ploidy and in some cancers amplicons may contain tens or hundreds of copies of an oncogene. Possible mechanisms generating amplification include extra-replication and recombination, breakage-fusion-bridge cycles, double rolling-circle replication, and replication fork stalling and template switching.

Copy number gain. Gain of a chromosomal segment or even whole chromosome/chromosome arm resulting in a regional copy number that exceeds the background genome ploidy.

Homozygous deletion. Bi-allelic loss of a segment of DNA arising through independent overlapping deletions involving both chromosomes. In contrast to heterozygous deletions where a single allele is deleted.

Tumour characteristics

Intra-tumour heterogeneity. The coexistence, within an individual cancer, of multiple sub-clonal populations of cancer cells that differ in their genomic, epigenomic, transcriptional, morphological or behavioural features. Intratumour heterogeneity includes ‘temporal heterogeneity’ whereby sub-clonal structure varies over time (including during treatment exposure) and ‘spatial heterogeneity’ whereby cancer sub-clones can show spatial variegation within a single primary tumour or metastatic deposit, between a primary tumour and metastatic deposit(s) or between multiple metastatic deposits.

Inter-tumour heterogeneity. Genomic, epigenomic, transcriptional, pathological or clinical differences between individuals’ cancers.

Clonal evolution. The mechanism by which a cancer develops from a once normal cell, through a reiterative process of mutation accumulation, clonal selection and clonal expansion. Mutation accumulation may be gradual and/or occur in a punctuated fashion.

Cancer clone. Cancer cells derived from the same ancestral cell. Clonally related cancer cells share all somatic mutations that were present within the most recent common ancestor—a term that refers to the last cell that is inferred to have existed during cancer evolution before sub-clonal diversification.

Cancer sub-clone. The progeny of a mutant cell arising within a cancer clone. What distinguishes a cancer sub-clone from the cancer clone is that only a fraction of the cancer cells present in the tumour derive from the ancestral cell of a sub-clone.

Circulating tumour cells. Cells that have been shed from a tumour into body fluids (i.e. blood, cerebrospinal fluid) and can provide information about the molecular characteristics of the tumour of the patient.

Cell free circulating tumour DNA. DNA derived from tumour cells that is found extracellular, circulating in bodily fluids (i.e. blood, cerebrospinal fluid) that can provide information about the molecular characteristics of the tumour of the patient.

Extracellular vesicles. Cell-derived nano-sized vesicles generated by cell membrane shedding or vesicle exocytosis that carry tumour-derived nucleic acids and proteins and can provide information about the molecular characteristics of the tumour of the patient.

Clinical trials and statistics

Basket trial. Biomarker-based, randomised or non-randomised clinical trial that includes multiple histologies investigating a therapeutic intervention, such as a drug or a drug combination targeting a specific molecular aberration across different cancer types. An example is a clinical trial of the BRAF inhibitor vemurafenib in multiple non-melanoma cancer types all harbouring

BRAF V600 mutations [13]. Within the context of a basket trial, sub-baskets can be stratified by histology.

Umbrella trial. Biomarker-based, randomised or non-randomised clinical trial that is histology-specific investigating different therapeutic interventions, such as different drugs or drug combinations, matched to different molecular aberrations in a single cancer type. An example is the FOCUS4 trial in patients with metastatic colorectal cancer that investigates multiple systemic therapies matched to specific molecular aberrations (EudraCT number: 2012-005111-12).

Adaptive trial. Clinical trial that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study. Analyses of the accumulating study data are carried out at prospectively planned time points within the study, can be carried out in a fully blinded manner or in an unblinded manner, and can occur with or without formal statistical hypothesis testing. An example is the I-SPY2 trial evaluating different neoadjuvant systemic regimens of novel agents in breast cancer (<https://clinicaltrials.gov/ct2/show/NCT01042379>) (20 October 2017, date last accessed).

N-of-one trial. Clinical trial of a single subject investigating a specific therapeutic intervention, such as a drug or a drug combination.

Spider plot. A spider plot is a graphical representation of the longitudinal percent change from baseline in the sum of typically RECIST-based tumour measurements over the period of subject evaluation, in which a leg of the spider corresponds to a study subject. The time points corresponding to appearances of new lesions can be highlighted by particular symbols.

Circos plot. A circos plot is a circular figure that can be used to represent molecular aberration data, in which genomic positions are depicted as ribbons. Each ring corresponds to the molecular data of a patient sorted by the genomic positions. Different types of molecular aberrations can be depicted on different layers of the circle. They can be drawn for genome-wide aberrations or only in more selected genome regions such as a chromosome.

Waterfall plot. A waterfall plot is a figure that displays the maximum percent change from baseline in the sum of the diameters of target lesions of the patients included in a study as measured by RECIST 1.1 or other criteria. To calculate the change from baseline in the target lesion diameter, patients need to have had measurable disease at baseline and a post-baseline measurement. Different colours are often used to highlight particular response categories or other characteristics.

Research tools

Liquid biopsy. Fluid biological samples (i.e. blood, cerebrospinal fluid, urine, saliva) that contain markers (i.e. circulating cells, cell-free circulating DNA, RNA, miRNA, proteins) that can

provide information about the molecular characteristics of the tumour of the patient.

Patient-derived xenograft models. Animal model where derived clinical tumour specimens are implanted in immuno-deficient mice (or other preclinical animal species).

Orthotopic animal models. Animal model where derived clinical tumour specimens are implanted in immuno-deficient mice (or other preclinical animal species) in the same anatomical location where the tumour from the patient was extracted.

Humanised animal mode. Animal model where derived clinical tumour specimens are implanted in immuno-deficient mice (or other preclinical animal species) in which elements of the human immune system have been reconstituted.

Tumouroids (tumour organoids). Cell cultures where derived clinical tumour specimens are cultured *in vitro* generating three dimensional molecular structures that can be passaged over time and that maintain some of the molecular characteristics of the original tumour. Tumouroids can be cultured from multiple cell lines (for example epithelial and stromal cells) to help mimic multicellular interactions within tumours.

Primary cultures. Cell cultures where derived clinical tumour specimens are freshly cultured *in vitro* for a few passages.

Organotypic cultures. Tissue cultures where derived clinical tumour specimens are sliced preserving the tissue structure and intratumour heterogeneity and cultured for short periods of time.

Syngenic animal models. Animal model where patient-derived tumour specimens from mice (or other preclinical animal species) are implanted in the same immuno-competent strain of mice where the tumour was originated.

Acknowledgements

We would like to thank all respondents to our survey, the ESMO Translational Research and Personalised Medicine Working Group for initiating the project and the ESMO staff Dr Svetlana Jezdic for help in running the project.

Funding

The Precision Medicine Glossary is a project funded by ESMO (no grant number applies).

Disclosure

AS and NN are supported by the Associazione Italiana Ricerca sul Cancro (NN Grant number IG17135). JSR-F, CS and FA are supported in part by the Breast Cancer Research Foundation. All remaining authors have declared no conflicts of interest.

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