



Precision oncology – Guideline of the Austrian, German and Swiss Societies for hematology and medical oncology

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ABSTRACT

Precision oncology is a multi-step process including patient selection, tumor profiling, molecular tumor board discussion and personalized cancer management. So far, it remains largely unstandardized. The implementation of precision oncology can be beneficial for patients but implementation differs widely between tumor types and local practices. A working group was established by the Austrian, German and Swiss societies for Hematology and Medical Oncology to establish an expert consensus on evidence-based standards and implementation of precision oncology. Herein, we present a summary of this guideline. The full documents are available at www.onkopedia-guidelines.info

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1. Introduction

The term "precision oncology" is used inconsistently and includes the use of targeted therapeutics, new sequencing techniques and tissue-agnostic therapy strategies based on molecular alterations. In this guideline, "precision oncology" refers to the use of broad molecular tumor characterization with the aim of personalized disease management.

Molecular testing and molecularly stratified therapies have already become standard for numerous tumor entities (e.g., non-small cell lung carcinoma NSCLC, colorectal carcinoma, hematological malignancies, etc.). For these cases, the respective entity-specific guidelines should be consulted.

However, in addition to guideline-based personalized oncology, effective treatment options can also be identified for patients with other tumor entities through molecular tumor analysis. This is illustrated by the increasing number of predictive biomarkers with cross-entity relevance.

Predictive biomarkers can be characterized by alterations in a few defined molecules (e.g., *BRAF* mutations, *NTRK* fusions) or as complex biomarkers based on the identification of numerous alterations (e.g., microsatellite instability (MSI), tumor mutational burden (TMB), or deficient homologous DNA recombination (HRD)). In addition, biomarkers can be detected in various analytes (DNA, RNA, protein) and by an increasing number of (high throughput) methods. For this reason, broad molecular analyses are often carried out to detect numerous potential biomarkers in parallel. In addition, alterations that are potentially therapeutically relevant but not covered by current guidelines can also be found as part of guideline-based molecular diagnostics.

The appropriate indication, test selection, and clinical interpretation of molecular alterations to facilitate evidence-based personalized therapy present a significant challenge, particularly given the frequent lack of robust clinical data. This complex process necessitates the involvement of multidisciplinary expertise, typically within the framework of specialized molecular tumor boards (MTB).

2. Materials and methods

The guidelines were developed by a working group established by the German, Austrian and Swiss Societies for Hematology and Oncology. In order to establish a scope of this newly developed guideline, a harmonized precision oncology workflow (Figure 1) was developed, followed by the establishment of evidence-based recommendations for each step within the workflow. The guideline together with a guideline report was published online [1].

The draft was independently reviewed and approved by society

representatives before publication, and finally approved by the entire guidelines working party.

2.1. Overview

The implementation and interpretation of comprehensive molecular testing demand a collaborative and multidisciplinary approach encompassing the appropriate selection of tests, molecular analysis, bioinformatics processing, interpretation of results, and their integration into clinical context to formulate actionable treatment recommendations [2]. A schematic summary is provided in Figure 1.

The reevaluation of molecular findings within an MTB is not universally required for all genomic alterations. Molecular alterations, which are well-defined in established clinical guidelines and drug approvals (e.g., canonical *EGFR* mutation in NSCLC, *BRAF* p.V600E mutation in melanoma, *RET* mutation in medullary thyroid carcinoma), should be addressed in multidisciplinary organ-specific tumor boards. However, complex or atypical findings that are not covered by tumor-specific guidelines and often identified in re-biopsies performed following prior standard-of-care treatments, warrant detailed interpretation and discussion in an MTB to ensure appropriate clinical integration and therapeutic decision-making (Figure 2).

2.2. Patient selection

Outside of clinical trials, the indication for molecular profiling should be based on a potential therapeutic relevance. Patient selection should be guided by the patient's eligibility for additional therapy, current clinical guidelines, approval status and availability of therapies, as well as the prevailing clinical and scientific evidence. Furthermore, the recommendation of a (molecular) tumor board should be considered to ensure a multidisciplinary and evidence-based approach to decision-making.

Molecular diagnostics are increasingly integrated in guideline-based standard workup for early treatment lines or relapsed disease, and are part of the standard diagnostics for the respective tumor entity. Examples include many driver alterations in NSCLC, *BRAF* mutations in melanoma and colorectal carcinoma, *HER2* amplifications in breast cancer, *RET* mutations in medullary thyroid carcinoma and many more. For these patients, following molecular diagnostics, presentation to an organ tumor board is usually sufficient.

Other indications for molecular diagnostics include the fulfillment of inclusion criteria for molecular-stratified clinical trials. Here, too, molecular diagnostics are increasingly moving into early lines of treatment. For example, the centers participating in the German national Network for Genomic Medicine Lung Cancer (nNGM) are integrating study-

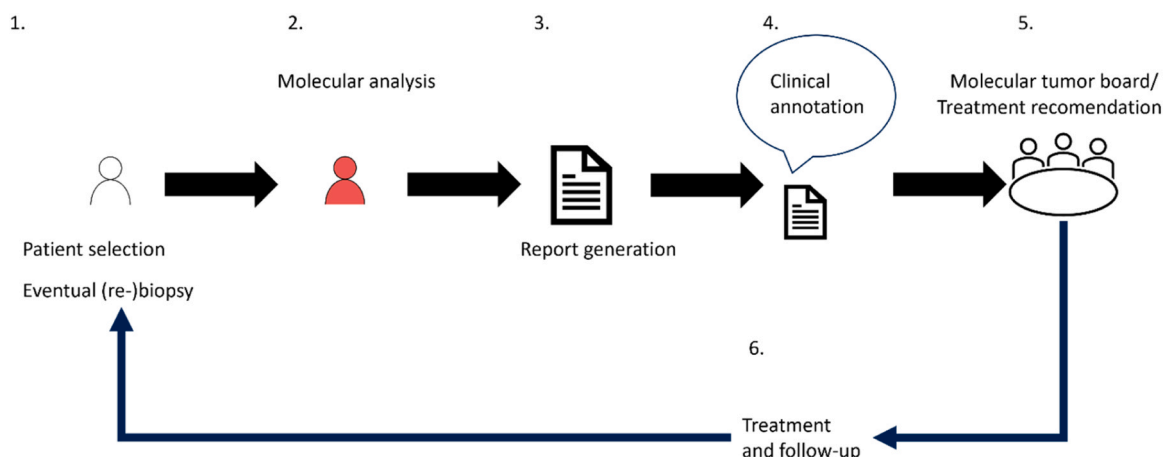


Fig. 1. Schematic overview of working steps in precision oncology.

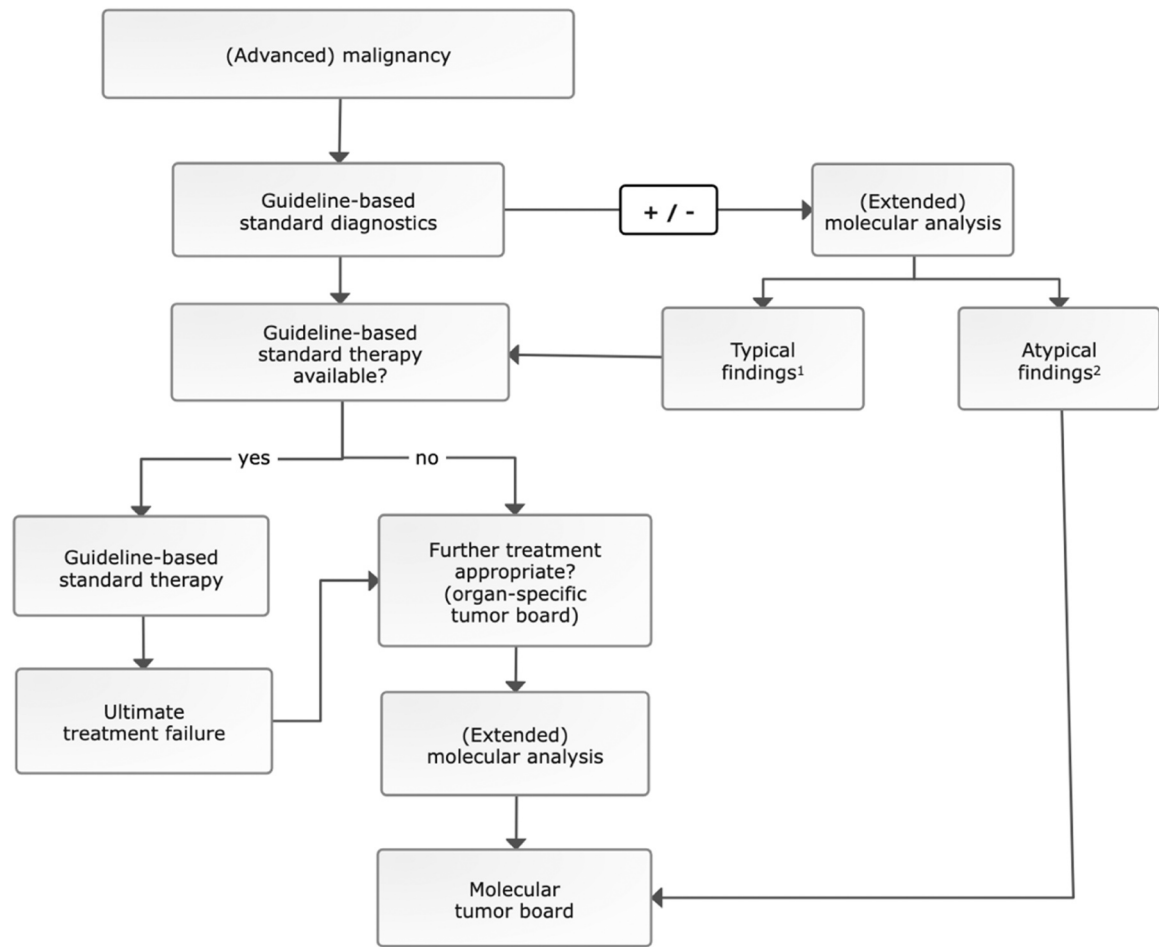


Fig. 2. Algorithm for integrating advanced molecular diagnostics into the clinical treatment/decision process. Figure legend: ¹ Biomarkers for a guideline-based treatment option; ² Potential biomarkers without guideline-based and/or without approved therapy option and/or alterations with unclear clinical consequences in the opinion of the treating physician(s); Comprehensive molecular diagnostics with subsequent discussion of the findings in a molecular tumor conference is carried out after guideline-based therapy options have failed in later therapy lines. Larger NGS panels are also increasingly used early in routine diagnostics, thus leading to atypical findings, warranting the involvement a molecular tumor conference at an earlier stage.

relevant molecular markers into their NGS-based primary diagnostics in addition to the approved molecular therapy options.

In patients who have failed standard therapies, including approved targeted therapies, the indication for (possibly extended) molecular diagnostics can be decided by an organ tumor board. The resulting findings should then be discussed in an MTB. Such MTBs are established at most comprehensive cancer centers (CCCs) and also increasingly at other cancer centers.

In accordance with the recommendations of the German Network for Personalized Medicine (DNPM), which are also included in the certification criteria for centers for personalized medicine (as defined by the German Cancer Society, DKG), the following inclusion criteria have been specified for access to MTBs (with corresponding comprehensive molecular characterization) (see Table 1).

A decision to order comprehensive molecular diagnostics, after standard therapies have failed, usually requires individual decision-making in a multidisciplinary tumor conference. Particularly in

patients with rapidly progressive tumor diseases, the choice of the appropriate method, the expected duration of the diagnostic procedures and the subsequent clinical implementation should be considered and corresponding analyses should therefore be initiated at an earlier stage.

Molecular characterization of tumors is being used increasingly as part of routine diagnostics and, based on current guidelines, also at an early stage of treatment, for example before the first-line therapy decision is made. For the majority of these cases, an MTB is not mandatory. However, with the expanding use of methods for parallel DNA and RNA sequencing of numerous gene regions, genetic aberrations with uncertain biological and clinical relevance (e.g., atypical *EGFR* mutations) or complex molecular alterations, such as the simultaneous presence of several potentially predictive biomarkers, are increasingly found. The clinical classification of such findings, as well as variants of unclear significance (VUS), may require the additional involvement of a MTB.

Figure 2 illustrates a possible flow chart for integrating broad molecular diagnostics or specialized discussion of findings into the clinical

Table 1
Access criteria for molecular tumor boards within the German Network for Personalized Medicine (DNPM) [25].

Criteria
Advanced or rare cancer
(Anticipated) Exhaustion of standard therapies
Feasibility of molecular-based therapy after assessment of clinical parameters
Agreement to a possible therapy based on the molecular findings

treatment/decision algorithm.

In addition to patient selection (see Table 1), the selection of the appropriate (tumor) material to be examined also plays a pivotal role. Both the representativeness of the available sample and the fixation technique must be taken into account. Table 2 lists criteria that can be used when deciding whether or not to perform a new biopsy.

In addition to re-sampling, liquid biopsy techniques can also be used for some indications. It should be noted that these have a high specificity for many markers, especially fusion genes and amplifications, but (still) have a lower sensitivity compared to tissue biopsies. Tissue diagnostics therefore remain the current standard, particularly in primary diagnosis, while liquid biopsy is increasingly being used in recurrence settings where biopsies are difficult to obtain, and for therapy monitoring as part of clinical trials.

2.3. Molecular analysis

Therapeutically relevant molecular alterations can be identified at numerous levels of cellular regulation (summarized in Table 3).

New technologies enable the rapid and simultaneous analysis of numerous potential biomarkers using high-throughput methods. In the field of precision oncology, DNA and RNA sequencing currently play the most important role alongside immunohistochemistry. Possible diagnostic procedures are summarized in Table 4 [3,4].

The selection of a suitable molecular diagnostic test should also take into account previous analyses and the pre-test probability of clinically relevant biomarkers (Tables 8 and 9).

2.4. Report generation

The performance of molecular testing and identification of molecular alterations is a largely standardized process and the domain of human genetics, (molecular) pathology and bioinformatics, among others, and should be carried out in a quality-assured environment, if possible, in an institute/laboratory accredited for molecular diagnostics. Ideally, molecular diagnostics should be embedded in a clinical environment that ensures the necessary multidisciplinary with regard to the interpretation and clinical annotation of the results.

The report should include information on the (tumor) material used, material quality, tumor cell content, type of analysis performed, listing of identified alterations in standardized coding, variant allele frequency and a functional evaluation of the variants. Human genetics must be included in the evaluation of potential germline variants.

The functional assessment of molecular alterations should be carried out on the basis of existing guidelines and SOPs (e.g. [5]).

2.5. Clinical annotation

Specific molecular alterations may contain relevant information for the clinical management of malignant diseases. The identification of

Table 2

Possible criteria for a decision for or against re-sampling. It should be noted that these criteria must be carefully weighed up and discussed in each individual case.

Analysis from existing tissue	Re-sampling
Tumor tissue from the current disease setting available	Tumor tissue from another disease situation (e.g., primary tumor before definitive therapy)
Primary resistance to last line of therapy without expected changes of molecular findings	Secondary resistance to last line of therapy with expected molecular change (e.g., targeted substances)
Planned molecular analysis from available material possible	Planned molecular analysis not possible from available material
Re-sampling not possible or inadequately harmful	Re-sampling is simple and at low-risk

Table 3

Summary of possible levels of genetic dysregulation.

Level of molecular alteration	Description	Detection
Gene variants	Alterations at the gene level that lead to a change or loss of function of the gene product via changes in the nucleic bases	Detection of alterations in the nucleic base sequence, e.g., using Sanger or next-generation sequencing (NGS)
Structural change	Alterations at the (sub-) chromosomal level leading to a change in function, loss of function or dysregulation of the gene product via fusion genes and copy number changes such as amplifications or deletions	Detection of structural chromosomal alterations, e.g., by means of fluorescence in situ hybridization (FISH) or mostly RNA-based next-generation sequencing
Epigenetic change	Alterations in regulatory elements such as DNA or histone modifications that lead to dysregulation of the gene product	Detection e.g., by bisulfite sequencing and/or methylation array
Quantitative gene product modification	Alterations in the amount of relevant gene products, such as protein overexpression	Detection of increased or decreased expression of gene products, e.g., using immunohistochemistry, proteomics, phosphoproteomics, multiplex technologies, RNA sequencing, Quantitative PCR, NanoString
Complex biomarkers	The number and type of the sum of molecular alterations can be quantified as complex biomarkers and evaluated, for example, as tumor mutational burden (TMB) or homologous recombination deficiency (HRD) scores as a separate biomarker	Detection via specific calculation methods based on DNA analyses

Table 4

Description of possible sequencing methods.

Procedure	Description
Single gene sequencing	Analysis of the base sequence of a single gene region, usually using Sanger sequencing, to identify gene mutations. This analysis is usually performed without parallel germline analysis as a control.
Gene panel sequencing	Parallel analysis of the base sequences of numerous gene regions using next-generation sequencing (NGS). Depending on the type and size of the gene panel, up to several hundred gene mutations and, in some cases, structural alterations such as amplifications can be detected simultaneously. RNA-based gene panels also allow the identification of fusion genes. Large gene panels also allow complex biomarkers such as tumor mutation load to be estimated. This analysis can be performed without parallel germline analysis as a control.
Exome sequencing	Parallel analysis of the base sequences of the protein-coding regions (exome) of the genome using NGS. This is used to detect gene mutations, copy number alterations and complex biomarkers. This analysis is carried out with parallel germline analysis as a control.
Genome sequencing	Parallel analysis of the base sequences of the entire genome using NGS. This is used to detect gene mutations, structural alterations and complex biomarkers. This analysis is carried out with parallel germline analysis as a control

these biomarkers is therefore the goal of molecular testing. The clinical annotation of a variant serves to evaluate it as a biomarker. Table 5 gives an overview of different classes of biomarkers [6]. An annotation as a

Table 5
Overview of different types of biomarkers.

Biomarkers	Description
Diagnostic	Information about the type of disease
Prognostic	Information about the course of the disease
Predictive	Information on the probability of response to a specific therapy
Pharmacogenomic	Information on pharmacokinetics and drug interactions
Predisposing	Information on the probability of the emergence of a certain disease

predictive biomarker often requires an extensive literature search. Numerous databases allow a simplified search for information. The content of the databases often does not overlap (e.g. civicdb.org, oncobk.org, <https://ckb.jax.org/>) and analysis of the primary literature is essential to classify the findings [7].

To evaluate the corresponding biomarker against the background of the respective tumor entity, evidence levels were defined, which should be used for assessment [8–10]. In German-speaking countries, the NCT/ZPM evidence levels are the most widely used (Table 6). In addition to these, there are other evidence levels such as AMP/ASCO/ACP [11] or ESMO-ESCAT [12].

There are increasing numbers of predictive biomarkers with tissue-agnostic approval for targeted drugs (corresponding to at least ESCAT Level I-C, NCT m1A, JCR Tier 1 A.1). Corresponding predictive biomarkers with FDA approval are shown in Table 7.

In Europe, there are currently two tissue-agnostic approvals for NTRK inhibitors and RET inhibitors (NTRK1–3 fusions or RET fusions).

Table 6
Evidence level according to NCT/ZPM.

Data source	Evidence level	Description
Same tumor entity	m1A	In the same tumor entity , the predictive value of the biomarker or clinical efficacy was demonstrated in a biomarker-stratified cohort of an adequately powered prospective study or meta-analysis .
	m1B	In the same tumor entity , the predictive value of the biomarker or the clinical efficacy was demonstrated in a retrospective cohort or case-control study .
	m1C	One or more case reports in the same tumor entity .
Other tumor entity	m2A	In another tumor entity , the predictive value of the biomarker or clinical efficacy was demonstrated in a biomarker-stratified cohort of an adequately powered prospective study or meta-analysis .
	m2B	In another tumor entity , the predictive value of the biomarker or clinical efficacy was demonstrated in a retrospective cohort or case-control study .
	m2C	Regardless of the tumor entity, clinical efficacy was demonstrated in one or more case reports when the biomarker was present.
In vitro or animal model	m3	Preclinical data (<i>in vitro/in vivo</i> models, functional studies) show an association of the biomarker with the efficacy of the drug(s), which is supported by a scientific rationale.
Biological rationale	m4	A scientific, biological rationale suggests an association of the biomarker with the efficacy of the drug(s), which is not yet supported by (pre)clinical data .

Additional references: is - In situ data from studies on patient material (e.g., IHC, FISH) support the level of evidence. The **supporting method** can also be indicated in brackets, e.g., evidence level 3 is (IHC). iv - In vitro data / in vivo models (e.g., PDX models) of the same tumor entity support the evidence level. The **supporting method** can be indicated in brackets, e.g., evidence level 2 iv (PDX). Z - additional reference for approval status (Z = EMA approval available; Z (FDA)= only FDA approval available) R - reference that this is a resistance marker for a specific therapy

Table 7
Overview of predictive biomarkers and associated treatment options with cross-entity efficacy and FDA approval.

Molecular alteration	Therapy
NTRK fusions	NTRK inhibition
RET fusion	RET inhibition
BRAF p.V600E mutation	BRAF inhibition (optionally + MEK inhibitor; + EGFR inhibition for colorectal carcinomas)
Mismatch repair deficiency (MSI-H / dMMR)	Immune checkpoint inhibition
High tumor mutational burden (TMB)	Immune checkpoint inhibition
HER2-positive (immunohistochemistry 3 +)	HER2-Antibody drug conjugate (ADC)

Table 8 summarizes the prevalence of these biomarkers (see Table 7) in various tumor entities. Table 9 summarizes the prevalence of additional biomarkers (NCT/ZPM evidence level 2).

2.6. Treatment recommendation/molecular tumor board

The final application of the identified and assessed biomarkers in the specific clinical situation requires broad multidisciplinary expertise and should be carried out preferentially by certified MTBs. According to the criteria of the German Network for Personalized Medicine (DNPM; [13]), the participating disciplines of an MTB team include at least hematology and medical oncology, pathology, molecular pathology, molecular biology, bioinformatics, human genetics as well as case-dependent specialist disciplines and radiology as required. In addition, this team should have sufficient and comprehensive expertise in the interpretation, evaluation and classification of molecular findings in the clinical context. To this end a sufficient number of MTB patients must be discussed by the team every year.

The high degree of individual variation and the different levels of evidence for the resulting recommendations require close attention to the clinical course and careful consideration when integrating any experimental treatment options into actual therapy beyond standard.

Ideally, non-approved treatment options should be administered within the framework of prospective clinical studies; the availability of such studies should therefore be evaluated as part of the treatment recommendation and assessed at least on a national level. However, implementation of the treatment recommendation often requires off-label use of medication. Here, the level of evidence for the recommended therapy should be taken into consideration with particular regard to the expected patient benefit. Off-label therapies should be followed up as part of registry studies (see below).

2.7. Follow Up

The high frequency of non-approved therapy recommendations and lack of clinical data supports the integration of research-based patient care in precision oncology. In particular, implementation rates of targeted therapies and treatment response to off-label therapies should be tracked and documented in a structured manner (see core data sets of the German Medical Informatics Initiative or the SPHN Swiss Personalized Oncology dataset in Switzerland). Ideally, this should be done as part of a prospective registry study and data should be pooled in a data network, as several scientific networks are currently making important contributions here. Consistent recording of molecular alterations can therefore also lead to an improved understanding of molecular pathomechanisms and effective treatment options.

3. Conclusion

Precision oncology comprises a multistep workflow that remains largely unstandardized. Yet, comprehensive tumor profiling, MTB

Table 8Population data from the AACR GENIE cohort^a [26].

Tumor entity	<i>BRAF</i> ^{V600E}	<i>RET</i> fusion	<i>NTRK</i> fusion	TMB-high (≥ 10 Mut/Mb)	MMRd/MSI-H	<i>HER2</i> positivity (IHC 3 +)
Ampullary carcinoma	1.1 % (n = 4)	0 % (n = 0)	5.1 % (n = 2)	19.3 % (n = 68)		
Anal carcinoma	0 % (n = 0)	2 % (n = 1)	2 % (n = 1)	19.9 % (n = 73)		
Appendiceal carcinoma	1.2 % (n = 9)	0 % (n = 0)	2.1 % (n = 1)	18.5 % (n = 137)		
Bladder carcinoma	0.1 % (n = 6)	0.3 % (n = 3)	1 % (n = 9)	38.8 % (n = 1813)	0.49 % (n = 2)	12.4 % (n = 59)
Breast cancer	0.1 % (n = 17)	0.4 % (n = 13)	1.4 % (n = 41)	11.7 % (n = 1874)	1.53 % (n = 16)	10.5 % (n = 388)
Cancer of unknown primary (CUP)	1.6 % (n = 86)	1 % (n = 8)	1.5 % (n = 12)	23.4 % (n = 1249)		2.1 % (n = 29)
Cervical carcinoma	0 % (n = 0)	0 % (n = 0)	0 % (n = 0)	18.2 % (n = 158)	2.62 % (n = 8)	3.9 % (n = 23)
Colorectal carcinoma	7.9 % (n = 1.228)	0.9 % (n = 15)	1.7 % (n = 29)	31.9 % (n = 4937)	14.47 % (n = 94)	1.8 % (n = 80)
Endometrial carcinoma	0.1 % (n = 4)	0.1 % (n = 1)	0.5 % (n = 4)	30.4 % (n = 1549)	31.37 % (n = 170)	3 % (n = 111)
Esophageal/gastric cancer	0.1 % (n = 6)	0.7 % (n = 8)	1.8 % (n = 20)	17.2 % (n = 817)	13.9 % (n = 87)	11.3 % (esophagus/GEJ n = 71), 4.7 % (gastric carcinoma, n = 27)
Gastrointestinal neuroendocrine tumors	3.7 % (n = 25)	0 % (n = 0)	5.4 % (n = 3)	6.6 % (n = 45)		0 % (n = 0/1136)
Gastrointestinal stromal tumor (GIST)	0.4 % (n = 6)	0 % (n = 0)	0.8 % (n = 1)	14.6 % (n = 226)		0 % (n = 0/143)
Germ cell tumor	0.1 % (n = 1)	0 % (n = 0)	1.1 % (n = 1)	2.9 % (n = 31)	0 % (n = 0/150)	2.4 % (n = 1)
Gliomas	3.9 % (n = 392)	0.3 % (n = 6)	1.8 % (n = 43)	11.1 % (n = 1121)	0.25 % (n = 1, GBM)	0 % (n = 0/41)
Head and neck squamous cell carcinomas	0.05 % (n = 1)	0.8 % (n = 2)	0.8 % (n = 2)	24.9 % (n = 548)	0.78 % (n = 4)	1.3 % (n = 7)
Hepatobiliary carcinomas	1.1 % (n = 39)	0.5 % (n = 3)	1.6 % (n = 10)	12 % (n = 413)	1.35 % (n = 1)	6.3 % (extrahepatic n = 5), 0.6 % (intrahepatic, n = 2), 0.4 % (hepatocellular n = 1)
Histiocytosis	17.3 % (n = 91)	8 % (n = 2)	0 % (n = 0)	2.7 % (n = 14)		
Melanoma	20.3 % (n = 1379) ^b	0.1 % (n = 1)	2.6 % (n = 18)	49.1 % (n = 3338)	0.64 % (n = 3)	0.1 % (n = 1)
Mesothelioma	0.1 % (n = 1)	0 % (n = 0)	1 % (n = 2)	2.8 % (n = 27)	2.41 % (n = 2)	
Non-small cell lung cancer (NSCLC)	1.4 % (n = 329)	5.7 % (n = 215)	0.9 % (n = 33)	33.8 % (n = 8142)	0.6 % (n = 6)	1.1 % (n = 49)
Ovarian cancer	0.9 % (n = 56)	0 % (n = 0)	0.6 % (n = 7)	12.8 % (n = 783)	1.37 % (n = 6)	1.6 % (epithelial, n = 122), 0.4 % (non-epithelial n = 1)
Pancreatic carcinoma	0.4 % (n = 26)	0.1 % (n = 1)	1.8 % (n = 15)	11.9 % (n = 820)	0 % (n = 0/183)	0.7 % (n = 14)
Parathyroid carcinoma	6.9 % (n = 2)	0 % (n = 0) ^c	0 % (n = 0) ^c	44.8 % (n = 13)	−0.8 % (n = 7/833)	
Penile carcinoma	0 % (n = 0)	0 % (n = 0)	0 % (n = 0)	25.4 % (n = 16)		0 % (n = 0/10)
Prostate carcinoma	0.02 % (n = 1)	0.2 % (n = 4)	0.4 % (n = 8)	5.4 % (n = 312)	0.6 % (n = 3)	0.6 % (n = 2/350)
Renal cell carcinoma	0 % (n = 0)	0.5 % (n = 1)	0 % (n = 0)	6.2 % (n = 160)	0.7 % (n = 5)	0 % (n = 0/531)
Salivary gland carcinoma	0.7 % (n = 7)	0.5 % (n = 1)	15.3 % (n = 29)	9.2 % (n = 93)		
Germ cord stromal tumors	0 % (n = 0)	0 % (n = 0)	0 % (n = 0)	4.6 % (n = 11)		
Non-melanocytic skin cancer	3.8 % (n = 46)	1.6 % (n = 3)	6.4 % (n = 12)	36.9 % (n = 448)		
Small intestine carcinoma	2.6 % (n = 12)	0 % (n = 0)	0 % (n = 0)	35.3 % (n = 164)		
Small cell lung cancer (SCLC)	0 % (n = 0)	0.7 % (n = 1)	0.7 % (n = 1)	35.8 % (n = 332)		0 % (n = 0/322)
Soft tissue sarcomas	0.3 % (n = 16)	0.3 % (n = 4)	2.3 % (n = 34)	5.8 % (n = 287)	0.78 % (n = 2)	0 % (n = 0/1211)
Thyroid carcinoma	40.2 % (n = 922)	36 % (n = 96)	17.2 % (n = 46)	10.1 % (n = 231)	0 % (n = 0/496)	0 % (n = 0/158)
Uterine sarcomas	0.1 % (n = 1)	0.6 % (n = 1)	2.3 % (n = 4)	6 % (n = 42)	3.51 % (n = 2)	
Vaginal carcinomas	0 % (n = 0)	0 % (n = 0)	0 % (n = 0)	21.6 % (n = 36)		
Vulvar carcinomas	0 % (n = 0) ^c	0 % (n = 0) ^c	0 % (n = 0) ^c	33.3 % (n = 1)		
Wilms tumor	2.1 % (n = 4)	0 % (n = 0)	0 % (n = 0)	4.7 % (n = 9)	2.44 % (n = 1)	

^a Data for MMRd/MSI-h and *HER2* positivity (IHC 3 +) are not available in the GENIE cohort and are derived from available publications [28,29]^b Higher *BRAF* p.V600E mutation frequencies in cutaneous melanoma have been described in previous publications (e.g., 39 %) [27]^c Gene might not have been profiled in this indication

Table 9
Prevalence of other molecular alterations (at least NCT evidence level 2) in various tumor entities. [17].

	ALK fusions	BRCA1 SNV	BRCA2 SNV	EGFR SNV	HER2 amplification	EGH2 SNV	FGFR2 fusions	FGFR3 SNV	FGFR3 fusions	IDH1 SNV	IDH2 SNV	KIT SNV	KRAS p-G12C	PDGFRA SNV	PIK3CA SNV	RET SNV	ROS1 fusions
Bladder carcinoma	0.1 %	1.3 %	2.2 %	2.5 %	4.3 %	0.6 %	0.1 %	21.9 %	2.0 %	0.2 %	0.1 %	0.1 %	0.4 %		19.4 %	0.1 %	
Breast cancer		1.3 %	1.9 %	1.3 %	10.4 %	0.3 %	0.2 %	0.1 %	0.1 %	0.1 %		0.3 %	0.1 %	0.2 %	38.1 %	0.1 %	0.1 %
Cervical carcinoma		1.1 %	0.9 %	0.2 %	2.1 %	0.3 %		0.9 %	0.6 %				0.5 %		27.6 %		0.2 %
Cholangiocarcinoma		0.7 %	2.0 %	1.1 %	2.2 %	0.4 %	7.3 %		0.4 %	14.5 %	3.5 %	0.1 %	1.0 %	0.3 %	4.5 %	0.1 %	0.2 %
Colorectal carcinoma	0.1 %	0.9 %	2.2 %	1.4 %	1.4 %	0.2 %	0.1 %	0.1 %		0.5 %	0.1 %	0.2 %	2.9 %	0.1 %	17.8 %	0.2 %	
Melanoma	0.1 %	0.9 %	1.4 %	0.9 %		1.1 %		0.1 %		2.6 %	0.3 %	3.9 %		0.8 %	2.2 %	0.1 %	0.1 %
Endometrial carcinoma		1.4 %	4.1 %	1.2 %	3.5 %	1.1 %	0.1 %	0.1 %	0.3 %	0.3 %		0.1 %	1.2 %	0.3 %	48.5 %	0.3 %	
Esophagogastric carcinoma		0.8 %	1.7 %	4.8 %	10.8 %	0.5 %	0.6 %	0.1 %	0.1 %	0.3 %	0.1 %	0.1 %	0.3 %	0.1 %	7.8 %	0.3 %	0.2 %
Gallbladder carcinoma		1.8 %	3.6 %	3.1 %	5.4 %				0.4 %	0.4 %			0.9 %		10.8 %		
GIST	0.1 %		0.1 %			0.1 %				0.1 %	0.1 %	78.9 %		10.3 %	1.3 %	0.1 %	
Head and neck squamous cell carcinoma	0.1 %	1.1 %	1.0 %	4.5 %	0.7 %	0.2 %	0.1 %	1.7 %	0.1 %	0.1 %	0.5 %	0.5 %	0.2 %	0.4 %	18.4 %	0.1 %	
NSCLC	2.0 %	0.6 %	0.9 %	26.9 %	0.8 %	0.3 %	0.1 %	0.1 %	0.1 %	0.3 %	0.1 %	0.4 %	11.3 %	0.3 %	5.2 %	0.1 %	0.8 %
Ovarian cancer	0.1 %	5.7 %	2.9 %	0.4 %	1.7 %	0.3 %	0.1 %		0.1 %		0.1 %	0.1 %		0.1 %	9.9 %	0.1 %	
Pancreatic carcinoma	0.2 %	0.6 %	2.4 %	0.2 %	0.7 %	0.2 %	0.2 %			0.2 %			1.1 %		2.1 %	0.1 %	0.2 %
Prostate carcinoma		0.5 %	5.0 %	0.4 %	0.1 %	0.3 %			0.1 %	0.4 %		0.1 %		0.1 %	3.8 %	0.1 %	0.1 %
Renal cell carcinoma	0.2 %	0.4 %	0.6 %	0.3 %		0.3 %		0.1 %				0.2 %	0.1 %	0.2 %	2.9 %	0.1 %	
Salivary gland carcinoma	0.8 %	0.6 %	0.5 %	0.5 %	4.6 %		0.1 %			0.5 %	0.1 %	1.4 %	0.1 %	1.3 %	8.7 %		0.3 %
Thyroid carcinoma	0.4 %	0.3 %	0.9 %	0.2 %		0.1 %	0.1 %	0.1 %		0.1 %		0.2 %	0.2 %	0.1 %	3.7 %	8.1 %	

discussion and personalized treatment initialization is increasingly implemented at many institutions [14]. The lack of harmonized workflows, limited access to personalized treatment options and rare molecular subgroups are a challenge for randomized controlled trials. Despite these limitations, recent clinical studies show a patient benefit with personalized tumor treatment [15,16]. These data and the approval of histology-agnostic, biomarker-stratified targeted treatments support the rational integration of molecular tumor profiling, which has also been recommended by ESMO and ASCO [17,18]. Other published recommendations include the evaluation of tumor-agnostic biomarkers and the use of evidence levels to guide treatment decisions [11,12,19–21]. Large overlaps but some specific differences exist between different evidence levels that should be considered when translating results between tumor boards [9]. A comparative table is provided in suppl. Table 1.

The purpose of this guideline is to establish a consensus across the multiple steps of a precision oncology workflow and facilitate local implementation. This clinical perspective leads to a relative underrepresentation of the molecular pathology workflow, for which additional separate recommendations should be considered [22–24]. Rapid technological developments including novel therapeutics, biomarkers and molecular profiling techniques, as well as the high level of multidisciplinary will require continuous updates of this guideline.

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Declaration of Competing Interest

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1. DTR employment Charité - Universitätsmedizin Berlin; advisory role BeiGene, J&J; Honoraria Roche, BMS, Bayer, Lilly; research funding Seagen; Other Bayer (travel support);
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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2025.115331](https://doi.org/10.1016/j.ejca.2025.115331).

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