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Precision Oncology

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

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Compliance rules:

- Guideline
- Conflict of interests

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1 Summary

The term "precision oncology" is used inconsistently and includes the use of targeted therapeutics, new sequencing methods 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 therapeutic management.

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

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 (*BRAF mutations*, *NTRK fusions*) or as complex biomarkers based on the identification of numerous alterations (microsatellite instability (MSI), tumor mutation 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 possible biomarkers. In addition, alterations potentially therapeutically relevant but not covered by current guidelines can also be found as part of guideline-based molecular diagnostics.

Adequate indication, test selection and clinical interpretation of molecular alterations with the aim of evidence-based personalized therapy, despite often limited clinical data, is a challenge and requires multidisciplinary expertise within the framework of specialized molecular tumor boards.

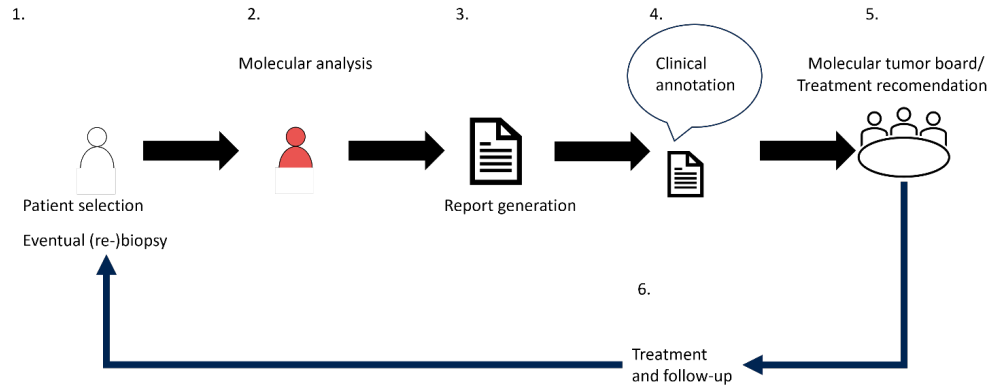
2 Basics

The performance and interpretation of broad molecular testing require multidisciplinary expertise. This includes the correct indication, the molecular analysis itself, its informational evaluation, the interpretation of the results and their classification in the clinical context with the aim of treatment recommendations [15]. A schematic sequence of work steps in precision oncology is shown in Figure 1.

If the indication is clear, i.e., based on guidelines and corresponding approval, it is sufficient to present the patient to a multidisciplinary organ tumor board (e.g., typical *EGFR* mutation in NSCLC, *BRAF p.V600E* mutation in melanoma, *RET* mutation in medullary thyroid carcinoma).

Complex findings not covered by guidelines, usually in the context of re-biopsies after prior standard treatment, should be presented to a molecular tumor board (MTB).

Figure 1: Schematic overview of work steps in precision oncology



3 Selection of patients

Outside of clinical trials, the indication for molecular diagnostics should always be based on the possible clinical relevance of the result. The patient's ability to undergo therapy, the current guidelines, the approval status of the therapy that may result from the diagnosis or the latest clinical and scientific findings and, if applicable, the decision of a (molecular) tumor board should be taken into account.

Molecular diagnostics are increasingly being included in guideline-based standard therapy for first-line treatment 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 colon 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 for the treatment decision.

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 national Network for Genomic Medicine Lung Cancer (nNGM) are integrating study-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 molecularly 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 a molecular tumor board. Such molecular tumor boards are established at most comprehensive cancer centers (CCCs) and increasingly also at other cancer centers.

In accordance with the recommendations of the German Network for Personalized Medicine (DNPM), which are also included in the OnkoZert certification criteria for centers for personalized medicine, the following inclusion criteria have been specified for access to molecular tumor boards (with corresponding broad molecular characterization) (Table 1)

Table 1: Access criteria for molecular tumor boards within the German Network for Personalized Medicine (DNPM) [9]

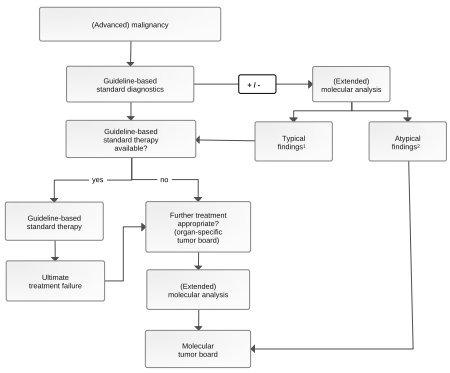
Criteria
Advanced or rare cancer
(Anticipated) Exhaustion of standard therapies
Feasibility of molecular-based therapy after assessment of clinical parameters
Agreement to a possible therapy based on the molecular findings

The decision to order extended 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 taken into account and corresponding analyses should therefore be initiated at an early stage.

Molecular characterization of tumors is increasingly being used 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. In the majority of these cases, a molecular tumor board is not necessary. However, with the increasing use of methods for parallel DNA and RNA sequencing of numerous gene regions, genetic aberrations whose biological and clinical relevance are not certain (example: atypical *EGFR* mutations) or complex molecular alterations such as the simultaneous presence of several potentially predictive biomarkers are also found. The clinical classification of such findings, as well as variants of unclear significance (VUS), may require the additional involvement of a molecular tumor board.

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

Figure 2: Algorithm for integrating advanced molecular diagnostics into the clinical treatment/ decision process



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); typically, extended 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. Increasingly, however, larger NGS panels are also being used early in routine diagnostics, with atypical findings such as rare variants or multi-layered molecular findings being identified time and again. This may also require the involvement a molecular tumor conference at an earlier stage.

In addition to patient selection (see Table 1), the selection of the appropriate (tumor) material to be examined also plays a 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 to take a new sample.

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
Repeat sampling not possible or inadequately harmful	Re-sampling is simple and at low-risk

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 diagnostics, while liquid biopsy is increasingly being used in recurrence settings where biopsies are difficult to obtain and is also increasingly being used for therapy monitoring as part of clinical studies.

4 Molecular analysis

Therapeutically relevant molecular alterations can be identified at numerous levels of cellular regulation. Table 3 summarizes possible levels of cellular dysregulation.

Table 3: Summary of possible levels of genetic dysregulation

Level of molecular alteration	Description	Proof
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	Proof via specific calculation methods based on DNA analyses

New technologies enable the rapid and simultaneous analysis of numerous possible 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 [1, 8].

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

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

5 Generation of report

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 multidisciplinarity 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., [6]).

6 Clinical annotation

Specific molecular alterations may contain relevant informations for the clinical management of malignant diseases. The identification of these biomarkers is therefore the goal of molecular testing. The clinical annotation of a variant serves to evaluate it as a biomarker. The following possible biomarkers can be distinguished (Table 5) [16].

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

An annotation as a 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, oncokb.org, https://ckb.jax.org/) and analysis of the primary literature is essential to classify the findings [14].

To evaluate the corresponding biomarker against the background of the respective tumor entity, evidence levels were defined, which should be used for assessment [7, 10, 13]. In German-speaking countries, the NCT/ZPM evidence levels are the most widely used. In addition to these, there are other evidence levels such as AMP/ASCO/ACP [11] or ESMO-ESCAT [12].

In addition to the interpretation of potential predictive biomarkers, other relevant biomarkers should also be assessed (e.g., DPYD diagnostics, if included). In the case of germline diagnostics, this requires the expertise and co-assessment of human genetics. Due to the high time expenditure and the necessary research work, the clinical classification and interpretation of the findings often takes place before the final decision on clinical application.

Table 6: Evidence level according to NCT/ZPM [10]

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** (*in vitro*/*in vivo* 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.**

Legend:

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

There are an increasing number 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 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; optionally + *EGFR* inhibition for colorectal carcinomas)
Mismatch repair deficiency (MSI-H / dMMR)	Immune checkpoint inhibition
High tumor mutation burden (TMB)	Immune checkpoint inhibition
HER2-positive (immunohistochemistry 3+)	HER2-Antibody drug conjugante (ADC)

Table 8 summarizes the prevalence of these biomarkers (see Table 7) in various tumor entities.

Table 8: Population data from the AACR GENIE cohort* [5]

Tumor entity	*BRAF*^{V600E}	*RET* fusion	*NTRK* fusion	TMB-high (≥ 10 Mut/Mb)	MMRd/MSI-H	*HER2* positivity (IHC 3+)
Ampullary carcinoma	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* = 1,813)	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* = 1,874)	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* = 1,249)		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 = 4,937)	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 = 1,549)	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 = 1,121)	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 = 1,379)[1]	0.1% (n = 1)	2.6% (n = 18)	49.1% (n = 3,338)	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 = 8,142)	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) -0.8% (n=7/833)	0.7% (n = 14)
Parathyroid carcinoma	6.9% (n = 2)	0% (n = 0)[a]	0% (n = 0)[a]	44.8% (n = 13)		

Tumor entity	*BRAF*^{V600E}	*RET* fusion	*NTRK* fusion	TMB-high (≥ 10 Mut/Mb)	MMRd/MSI-H	*HER2* positivity (IHC 3+)
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)	0% (n = 0)	0% (n = 0)	33.3% (n = 1)		
Wilms tumor	2.1% (n = 4)	0% (n = 0)	0% (n = 0)	4.7% (n = 9)	2.44% (n=1)	

Legend:
[1] Higher BRAF p.V600E mutation frequencies in cutaneous melanoma have been described in previous publications (e.g., 39%) [3].
**Data for MMRd/MSI-h and HER2 positivity (IHC 3+) are not available in the GENIE cohort and are derived from available publications [2, 17].*

Table 9: Prevalence of other molecular alterations (at least NCT evidence level 2) in various tumor entities. (according to: [4])

	ALK fusions	*BRCA1* SNV	*BRCA2* SNV	*EGFR* SNV	*HER2* ampli-fica-tion	*EZH2* 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 carci-noma	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	n/a	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 carci-noma	n/a	1.1%	0.9%	0.2%	2.1%	0.3%		0.9%	0.6%				0.5%		27.6%		0.2%
Cholan-giocarci-noma	n/a	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 carci-noma	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	0.2%	0.9%	1.4%	0.9%		1.1%		0.1%		2.6%	0.3%	3.9%		0.8%	2.2%	0.1%	0.1%
Endome-trial carci-noma	n/a	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%	
Esopha-gogastric carci-noma	n/a	0.8%	1.7%	4.8%	10.8%	0.5%	0.6%	0.1%	0.1%		0.1%	0.1%	0.3%	0.1%	7.8%	0.3%	0.2%
Gallblad-der carci-noma	n/a	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 carci-noma	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%	0.4%	0.1%	9.9%	0.1%	
Pancreatic carci-noma	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 carci-noma	n/a	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 carci-noma	0.2%	0.4%	0.6%	0.3%		0.3%		0.1%				0.2%	0.1%	0.2%	2.9%		
Salivary gland car-cinoma	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 carci-noma	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%	

7 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 by designated or certified molecular tumor boards. According to the criteria of the German Network for Personalized Medicine (DNPM; [9]), 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 course of therapy, which is ensured by a sufficient number of MTB patients.

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 further therapy.

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 particular consideration with regard to the expected patient benefit. Off-label therapies should be followed up as part of registry studies (see below).

8 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 extensively tracked and documented in a structured manner (see core data sets of the Medical Informatics Initiative). 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 also for less common malignancies in the future.

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16 Disclosure of Potential Conflicts of Interest

according to the rules of DGHO, OeGHO, SGH+SSH, SGMO

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