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ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO Recommendations on clinical reporting of genomic test results for solid cancers

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Background: Genomic tumour profiling has a crucial role in the management of patients with solid cancers, as it helps selecting and prioritising therapeutic interventions based on prognostic and predictive biomarkers, as well as identifying markers of hereditary cancers. Harmonised approaches to interpret the results of genomic testing are needed to support physicians in their decision making, prevent inequalities in precision medicine and maximise patient benefit from available cancer management options.

Methods: The European Society for Medical Oncology (ESMO) Translational Research and Precision Medicine Working Group assembled a group of international experts to propose recommendations for preparing clinical genomic reports for solid cancers. These recommendations aim to foster best practices in integrating genomic testing within clinical settings. After review of available evidence, several rounds of surveys and focused discussions were conducted to reach consensus on the recommendation statements. Only consensus recommendations were reported. Recommendation statements were graded in two tiers based on their clinical importance: level A (required to maintain common standards in reporting) and level B (optional but necessary to achieve ideal practice).

Results: Genomics reports should present key information in a front page(s) followed by supplementary information in one or more appendices. Reports should be structured into sections: (i) patient and sample details; (ii) assay and data analysis characteristics; (iii) sample-specific assay performance and quality control; (iv) genomic alterations and their

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functional annotation; (v) clinical actionability assessment and matching to potential therapy indications; and (vi) summary of the main findings. Specific recommendations to prepare each of these sections are made.

Conclusions: We present a set of recommendations aimed at structuring genomics reports to enhance physician comprehension of genomic profiling results for solid cancers. Communication between ordering physicians and professionals reporting genomic data is key to minimise uncertainties and to optimise the impact of genomic tests in patient care.

Key words: precision medicine, genomics, targeted therapies, next-generation sequencing (NGS)

INTRODUCTION

Genomic tumour profiling has entered cancer care, playing a pivotal role in the diagnostic and therapeutic management of cancer. Over the past decade, the number of drug approvals linked to genomic biomarkers has risen substantially. There remains, however, a gap between evidence generation and real-world clinical implementation of validated genomic biomarkers.[1] Addressing challenges in access to genomic testing and consequent treatment with biomarker-matched drugs, and in harmonised and structured analysis and interpretation of genomic data, is urgently needed to deliver the promise of precision oncology in clinical practice, but also to prevent genomic testing from further exacerbating health care inequities in our society.

Several guidelines and consensus recommendations, including those from the ESMO Precision Medicine Working Group (PMWG),[2] have been published to guide the use of next-generation sequencing (NGS) tests across different tumour types. NGS assays generate ample amounts of data, often interrogating large numbers of genes. Analysis and interpretation of these data are often complex, necessitating resources to assist both health care providers and patients in comprehending the results. Difficulties in interpreting genomic test results have been consistently identified as a factor that hinders their clinical adoption.[3,4] Physicians interpret NGS results from reports that summarise the findings which are usually prepared by the laboratory carrying out the sequencing. These reports should contain the information needed to empower physicians to integrate genomics into their clinical decision making, and the content should be clear, concise and intuitively understandable to make the process effective.

The workflow of precision oncology

The pathway for delivering precision oncology encompasses a series of actions (Figure 1), starting with patient information and shared decision making, as well as selection and acquisition of the most appropriate biospecimen for study. Once DNA/RNA from a tumour biospecimen (or blood sample in the case of liquid biopsies) and, when appropriate, matched normal sample has been sequenced, the raw NGS data are processed to identify genomic alterations. This task requires the use of bioinformatics to—among others—align the NGS reads to the human reference genome and identify differences in the reads between tumour and normal sequences (tumour variant calling). For assays with paired tumour—normal sequencing, the somatic origin of gene variants (base substitutions and small insertions or deletions; sometimes referred to as 'mutations') is determined by comparing the genomic sequence of the tumour sample with the genome of the healthy/non-cancerous tissue of the same patient. For tumour-only sequencing (that is, healthy/non-cancerous control tissue is not being analysed in parallel), the origin of the variants is estimated by comparison with population allele frequencies in data repositories, often in the context of the variant allele fractions observed in the tumour sample. Next, genomic mapping tools are used to calculate which gene or noncoding region is affected by each variant, and—if relevant—how they alter the nucleotide sequence of the corresponding transcripts and the amino acid sequence of the encoded proteins. These events are classified according to their biological relevance in terms of impact on protein function and potential role in carcinogenesis.[5,6] Genomic alterations are then ranked based on their clinical actionability, identifying biomarkers associated with cancer diagnosis, prognosis and drug response or resistance.[7,8] In addition, some NGS assays enable to estimate complex biomarkers or genomic signatures, such as tumour mutational burden (TMB), microsatellite instability (MSI) or homologous recombination deficiency (HRD) scores; liquid biopsies can also provide estimates of tumour burden with prognostic value in several tumour types. While most of these steps can be largely automated,[9,10] expert manual curation is still required to ensure the quality of the results. Finally, all the information obtained with NGS is structured into a report intended for delivery to physicians (and often to patients), which is the subject of this Recommendations document.

It is important to note that the content of an NGS report cannot replace the physician's judgement for indicating a therapeutic strategy. Clinical decision making should be driven by a patient-centric interpretation of the NGS assay results by the treating physicians, ideally with support from a multidisciplinary team, in the context of the results of other tests, as well as the individual patient's medical history and preferences.[11]

The precision medicine journey continues with assessing if genomics-guided treatment resulted in patient benefit, as that is the final goal of this process. Ideally, genomics, imaging and pathology test results, together with treatment information and clinical outcomes, would be systematically collected to inform future treatment decisions and iteratively improve the precision oncology workflow.

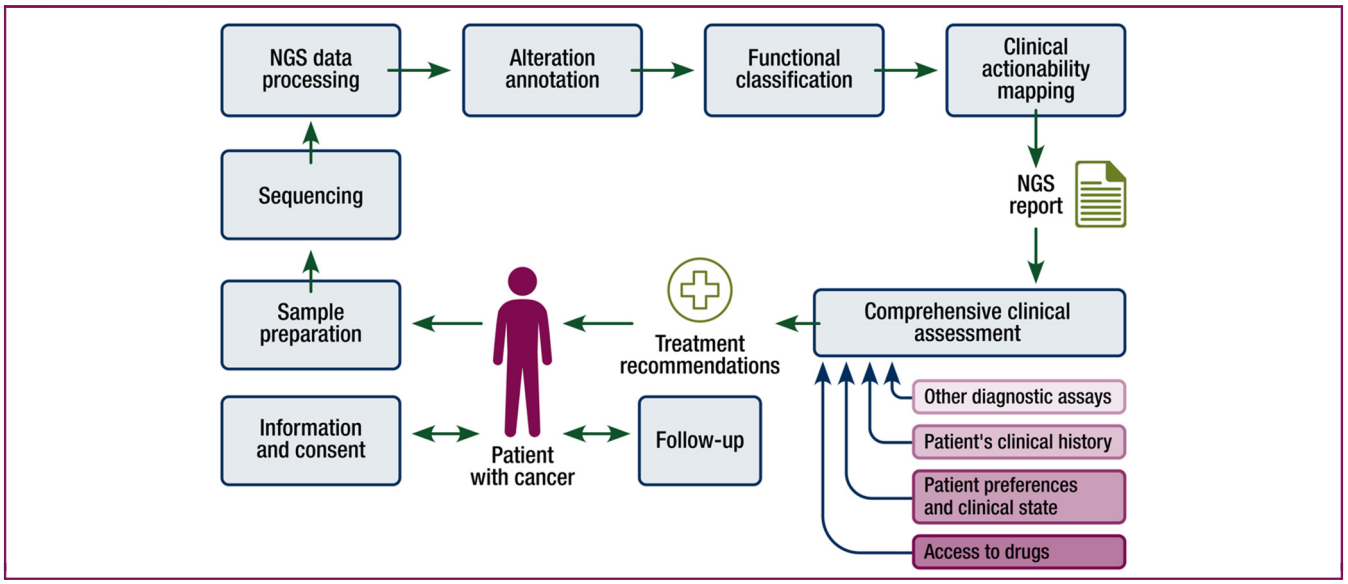

Figure 1. **Steps enabling clinical decision making based on NGS data. NGS, next-generation sequencing.**

Structure and content of a genomic report: Recommendations from the ESMO Precision Medicine Working Group

The ESMO PMWG convened a multidisciplinary group of international experts with expertise in generating, analysing, reporting and/or using genomic data for clinical purposes to formulate recommendations for the optimal reporting of genomic data intended for clinical use. The panellists first completed several surveys to identify unmet needs and key challenges in reporting genomic data, followed by several rounds of panel meetings to define recommendations; initial recommendation statements were then subject to several rounds of off-line review and in-person/remote live meetings by the group until consensus was reached for all statements. The group's objectives were to deliver recommendations regarding the structure and elements of this report to (i) facilitate comprehension of genomic reports among physicians and other health care professionals integrated in multidisciplinary tumour boards; (ii) improve communication among health care professionals and between physicians and patients regarding the interpretation of genomic data; and (iii) guarantee the quality of genomic test reporting.

A genomic report may include both text and tables to convey the findings of a tumour NGS test. The use of graphical solutions to display complex information is also recommended to increase intuitive comprehension by clinical readers. Reports must include the following information:

1. Patient, tumour and sample characteristics
2. NGS assay and data analysis characteristics
3. Sample-specific assay performance and quality control
4. Genomic alterations (somatic and/or germline) and other genomic measures detected in the tumour sample
5. Variant functional annotation
6. Matching with genomic biomarkers of cancer diagnosis, prognosis and therapy indication, ranked by clinical actionability
7. Summary of the main clinically relevant findings
8. Appendices with detailed information and references

These parts of the report, which will be discussed throughout the present document, may involve large amounts of information, particularly when it comes to technical aspects of the assay utilised. To facilitate readability by treating physicians, it is recommended to clearly provide all key information upfront in the first pages of the report, followed by other sections with expanded details. To illustrate how the recommendation can be used to provide an NGS report, an example report is given in Figure 2.

In addition to these recommendations, laboratories preparing NGS reports should also adhere to relevant quality principles, such as those outlined by the International Organization for Standardization or equivalent accreditations, to ensure that their reports meet the necessary standards for clinical applications in their local environment.

The group recognises the complexities in the analysis and reporting of genomic data for clinical applications and acknowledges that there may be variability in preferences and resources available across different laboratories, institutions and health care systems. Consequently, we have categorised our recommendations into two levels: Level A Recommendations, which we deem necessary for maintaining a common standard of quality in the reporting process; and Level B Recommendations, which represent ideal practices but can be selectively prioritised when facing resource constraints or when laboratories necessitate a more flexible approach. Thus, for clarity, the level of recommendation does not reflect the level of consensus among the panellists but the level of clinical relevance of each recommendation.

The overarching goal of this Recommendation document is to advance in the delivery of precision oncology,

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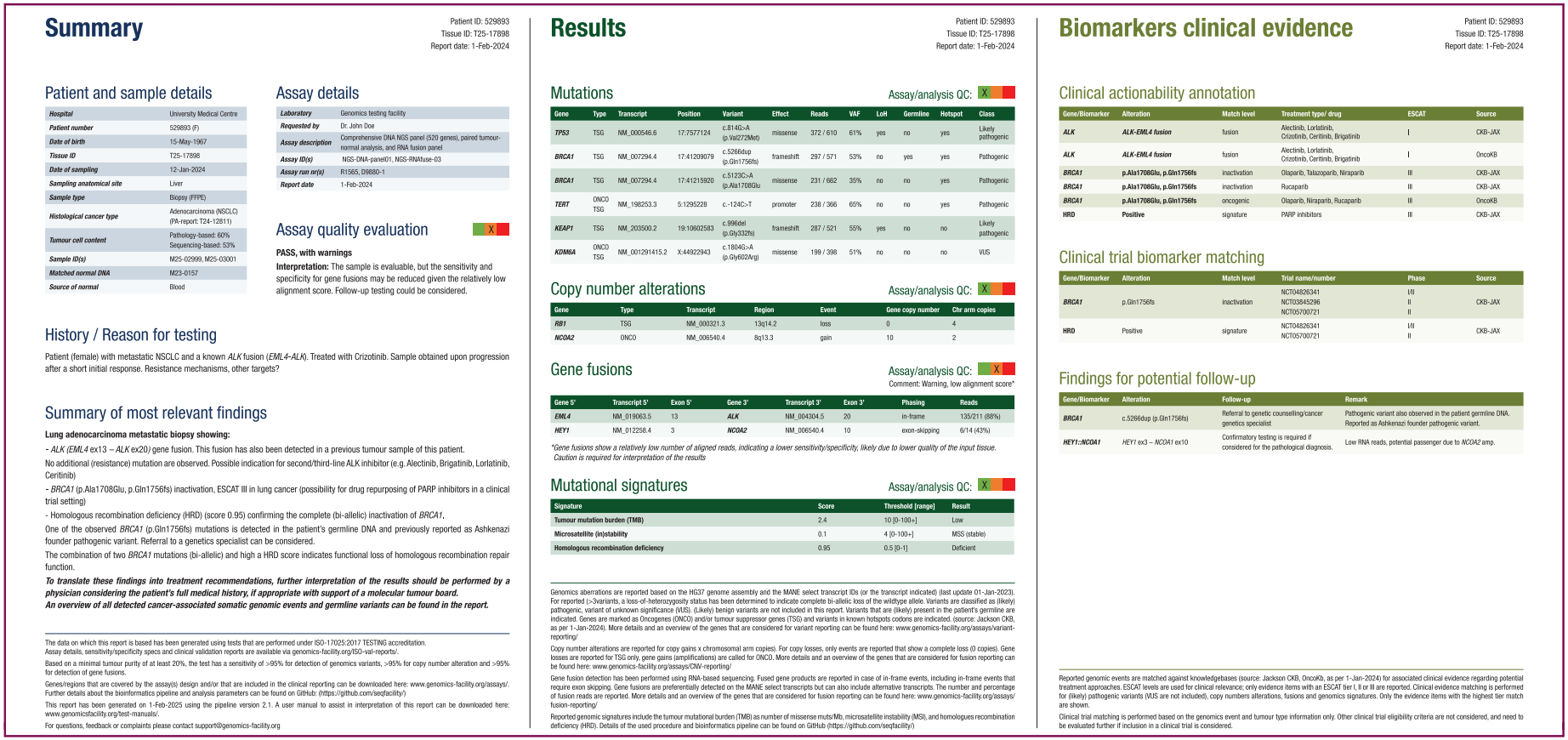

Summary

Patient ID: 529893
Tissue ID: T25-17898
Report date: 1-Feb-2024

Patient and sample details

Hospital	University Medical Centre
Patient number	529893 (F)
Date of birth	15-May-1967
Tissue ID	T25-17898
Date of sampling	12-Jan-2024
Sampling anatomical site	Liver
Sample type	Biopsy (FFPE)
Histological cancer type	Adenocarcinoma (NSCLC) (PA-report: T24-12811)
Tumour cell content	Pathology-based: 60% Sequencing-based: 53%
Sample ID(s)	M25-02999, M25-03001
Matched normal DNA	M23-0157
Source of normal	Blood

Assay details

Laboratory	Genomics testing facility
Requested by	Dr. John Doe
Assay description	Comprehensive DNA NGS panel (520 genes), paired tumour-normal analysis, and RNA fusion panel
Assay ID(s)	NGS-DNA-panel01, NGS-RNAfuse-03
Assay run nr(s)	R1565, D9880-1
Report date	1-Feb-2024

Assay quality evaluation

PASS, with warnings

Interpretation: The sample is evaluable, but the sensitivity and specificity for gene fusions may be reduced given the relatively low alignment score. Follow-up testing could be considered.

History / Reason for testing

Patient (female) with metastatic NSCLC and a known *ALK* fusion (*EML4-ALK*). Treated with Crizotinib. Sample obtained upon progression after a short initial response. Resistance mechanisms, other targets?

Summary of most relevant findings

Lung adenocarcinoma metastatic biopsy showing:

- *ALK (EML4* ex13 – *ALK* ex20*)* gene fusion. This fusion has also been detected in a previous tumour sample of this patient.

No additional (resistance) mutation are observed. Possible indication for second/third-line ALK inhibitor (e.g. Alectinib, Brigatinib, Lorlatinib, Ceritinib)

- *BRCA1* (p.Ala1708Glu, p.Gln1756fs) inactivation, ESCAT III in lung cancer (possibility for drug repurposing of PARP inhibitors in a clinical trial setting)

- Homologous recombination deficiency (HRD) (score 0.95) confirming the complete (bi-allelic) inactivation of *BRCA1*.

One of the observed *BRCA1* (p.Gln1756fs) mutations is detected in the patient's germline DNA and previously reported as Ashkenazi founder pathogenic variant. Referral to a genetics specialist can be considered.

The combination of two *BRCA1* mutations (bi-allelic) and high a HRD score indicates functional loss of homologous recombination repair function.

To translate these findings into treatment recommendations, further interpretation of the results should be performed by a physician considering the patient's full medical history, if appropriate with support of a molecular tumour board.
An overview of all detected cancer-associated somatic genomic events and germline variants can be found in the report.

The data on which this report is based has been generated using tests that are performed under ISO-17025:2017 TESTING accreditation.
Assay details, sensitivity/specificity specs and clinical validation reports are available via genomics-facility.org/ISO-val-reports/.

Based on a minimal tumour purity of at least 20%, the test has a sensitivity of >95% for detection of genomics variants, >95% for copy number alteration and >95% for detection of gene fusions.

Genes/regions that are covered by the assay(s) design and/or that are included in the clinical reporting can be downloaded here: www.genomics-facility.org/assays/. Further details about the bioinformatics pipeline and analysis parameters can be found on GitHub: (https://github.com/seqfacility/)

This report has been generated on 1-Feb-2025 using the pipeline version 2.1. A user manual to assist in interpretation of this report can be downloaded here: www.genomicsfacility.org/test-manuals/.

For questions, feedback or complaints please contact support@genomics-facility.org

Results

Patient ID: 529893
Tissue ID: T25-17898
Report date: 1-Feb-2024

Mutations

Assay/analysis QC:

Gene	Type	Transcript	Position	Variant	Effect	Reads	VAF	LoH	Germline	Hotspot	Class
TP53	TSG	NM_000546.6	17:7577124	c.814G>A (p.Val272Met)	missense	372 / 610	61%	yes	no	yes	Likely pathogenic
BRCA1	TSG	NM_007294.4	17:41209079	c.5266dup (p.Gln1756fs)	frameshift	297 / 571	53%	no	yes	yes	Pathogenic
BRCA1	TSG	NM_007294.4	17:41215920	c.5123C>A (p.Ala1708Glu	missense	231 / 662	35%	no	no	yes	Pathogenic
TERT	ONCO TSG	NM_198253.3	5:1295228	c.-124C>T	promoter	238 / 366	65%	no	no	yes	Pathogenic
KEAP1	TSG	NM_203500.2	19:10602583	c.996del (p.Gly332fs)	frameshift	287 / 521	55%	yes	no	no	Likely pathogenic
KDM6A	ONCO TSG	NM_001291415.2	X:44922943	c.1804G>A (p.Gly602Arg)	missense	199 / 398	51%	no	no	no	VUS

Copy number alterations

Assay/analysis QC:

Gene	Type	Transcript	Region	Event	Gene copy number	Chr arm copies
RB1	TSG	NM_000321.3	13q14.2	loss	0	4
NCOA2	ONCO	NM_006540.4	8q13.3	gain	10	2

Gene fusions

Assay/analysis QC:
Comment: Warning, low alignment score*

Gene 5'	Transcript 5'	Exon 5'	Gene 3'	Transcript 3'	Exon 3'	Phasing	Reads
EML4	NM_019063.5	13	***ALK***	NM_004304.5	20	in-frame	135/211 (88%)
HEY1	NM_012258.4	3	***NCOA2***	NM_006540.4	10	exon-skipping	6/14 (43%)

**Gene fusions show a relatively low number of aligned reads, indicating a lower sensitivity/specificity, likely due to lower quality of the input tissue. Caution is required for interpretation of the results*

Mutational signatures

Assay/analysis QC:

Signature	Score	Threshold [range]	Result
Tumour mutation burden (TMB)	2.4	10 [0-100+]	Low
Microsatellite (in)stability	0.1	4 [0-100+]	MSS (stable)
Homologous recombination deficiency	0.95	0.5 [0-1]	Deficient

Genomics aberrations are reported based on the HG37 genome assembly and the MANE select transcript IDs (or the transcript indicated) (last update 01-Jan-2023). For reported (>3variants, a loss-of-heterozygosity status has been determined to indicate complete bi-allelic loss of the wildtype allele. Variants are classified as (likely) pathogenic, variant of unknown significance (VUS). (Likely) benign variants are not included in this report. Variants that are (likely) present in the patient's germline are indicated. Genes are marked as Oncogenes (ONCO) and/or tumour suppressor genes (TSG) and variants in known hotspots codons are indicated. (source: Jackson CKB, as per 1-Jan-2024). More details and an overview of the genes that are considered for variant reporting can be found here: www.genomics-facility.org/assays/variant-reporting/

Copy number alterations are reported for copy gains x chromosomal arm copies). For copy losses, only events are reported that show a complete loss (0 copies). Gene losses are reported for TSG only, gene gains (amplifications) are called for ONCO. More details and an overview of the genes that are considered for fusion reporting can be found here: www.genomics-facility.org/assays/CNV-reporting/

Gene fusion detection has been performed using RNA-based sequencing. Fused gene products are reported in case of in-frame events, including in-frame events that require exon skipping. Gene fusions are preferentially detected on the MANE select transcripts but can also include alternative transcripts. The number and percentage of fusion reads are reported. More details and an overview of the genes that are considered for fusion reporting can be found here: www.genomics-facility.org/assays/fusion-reporting/

Reported genomic signatures include the tumour mutational burden (TMB) as number of missense muts/Mb, microsatellite instability (MSI), and homologues recombination deficiency (HRD). Details of the used procedure and bioinformatics pipeline can be found on GitHub (https://github.com/seqfacility/)

Biomarkers clinical evidence

Patient ID: 529893
Tissue ID: T25-17898
Report date: 1-Feb-2024

Clinical actionability annotation

Gene/Biomarker	Alteration	Match level	Treatment type/ drug	ESCAT	Source
ALK	***ALK-EML4 fusion***	fusion	Alectinib, Lorlatinib, Crizotinib, Ceritinib, Brigatinib	I	CKB-JAX
ALK	***ALK-EML4 fusion***	fusion	Alectinib, Lorlatinib, Crizotinib, Ceritinib, Brigatinib	I	OncoKB
BRCA1	**p.Ala1708Glu, p.Gln1756fs**	inactivation	Olaparib, Talazoparib, Niraparib	III	CKB-JAX
BRCA1	**p.Ala1708Glu, p.Gln1756fs**	inactivation	Rucaparib	III	CKB-JAX
BRCA1	**p.Ala1708Glu, p.Gln1756fs**	oncogenic	Olaparib, Niraparib, Rucaparib	III	OncoKB
HRD	**Positive**	signature	PARP inhibitors	III	CKB-JAX

Clinical trial biomarker matching

Gene/Biomarker	Alteration	Match level	Trial name/number	Phase	Source
BRCA1	p.Gln1756fs	inactivation	NCT04826341 NCT03845296 NCT05700721	I/II II II	CKB-JAX
HRD	Positive	signature	NCT04826341 NCT05700721	I/II II	CKB-JAX

Findings for potential follow-up

Gene/Biomarker	Alteration	Follow-up	Remark
BRCA1	c.5266dup (p.Gln1756fs)	Referral to genetic counselling/cancer genetics specialist	Pathogenic variant also observed in the patient germline DNA. Reported as Ashkenazi founder pathogenic variant.
HEY1::NCOA1	*HEY1* ex3 – *NCOA1* ex10	Confirmatory testing is required if considered for the pathological diagnosis.	Low RNA reads, potential passenger due to *NCOA2* amp.

Reported genomic events are matched against knowledgebases (source: Jackson CKB, OncoKb, as per 1-Jan-2024) for associated clinical evidence regarding potential treatment approaches. ESCAT levels are used for clinical relevance: only evidence items with an ESCAT tier I, II or III are reported. Clinical evidence matching is performed for (likely) pathogenic variants (VUS are not included), copy numbers alterations, fusions and genomics signatures. Only the evidence items with the highest tier match are shown.

Clinical trial matching is performed based on the genomics event and tumour type information only. Other clinical trial eligibility criteria are not considered, and need to be evaluated further if inclusion in a clinical trial is considered.

Figure 2. Example of a genomics report consolidating findings derived from paired tumour/normal testing.

while upholding the principles of quality and equity in patient care. Considering the differences in the genomic landscape and clinical management of haematological malignancies, this document is focused on the reporting of NGS test results for the management of solid malignancies. In addition, while we acknowledge that targeted gene panels are currently the most common form of multi-gene NGS testing in clinical routine, this document is also relevant when reporting data from whole-exome sequencing (WES) or whole-genome sequencing (WGS) assays, which are progressively incorporated into clinical practice.

Recommendations

- Genomic reports should include the following information: Patient and sample characteristics; assay and data analysis characteristics; sample-specific assay performance; observed genomic alterations and other genomic measurements; and implications for diagnosis, prognosis and therapy selection. (Level A)
- We recommend division of the genomic report into an upfront part including all the key information that enables clinical interpretation, followed by other sections where further details can be provided. (Level A)
- We recommend including a summary statement in a narrative form with the main findings of the NGS assay. (Level A)
- We recommend considering the inclusion of visual aids and graphic solutions in genomic reports to facilitate comprehension of complex data. (Level B)

SECTION 1. SAMPLE AND PATIENT CHARACTERISTICS

Clinical genomic reports should start with a section detailing essential clinical, demographics and sample characteristics. The purposes are to enable accurate identification and tracking of the biospecimen, and to help contextualise genomic results.

Information about the patient

Essential clinical and demographic information should include patient identifier, age or date of birth, sex and the primary tumour type/disease under study. Additionally, including ethnicity and/or genetic ancestry data (when available) may be relevant for certain measurements using population allele frequencies, as those derive from studies where certain ethnicities are underrepresented. Critically, the inclusion of this information in the report should be done in compliance with the relevant personal data protection regulations. Details on the requesting physician/institution should also be added here.

Information about the biospecimen

Essential description of the sample under analysis should include a sample identifier, date of sample acquisition and modality of the sample (e.g. tumour tissue biopsy, cytological specimen, surgical resection specimen or blood/plasma/cerebrospinal fluid). For tissue samples, the anatomical origin (organ) and whether the sample comes from a primary or metastatic tumour, along with information about the tissue preservation mode [e.g. formalin-fixed paraffin-embedded (FFPE) or frozen tissue] should be included. For paired tumour—normal sample sequencing tests, the source of the normal DNA should also be described.

We recommend that tissue biospecimens also undergo histopathological evaluation concurrently with NGS testing for optimal interpretation. Every clinical genomic report should feature the histological disease subtype (according to standardised classification systems), as well as a pathology-based estimation of tumour content for the sample under study. Ideally, histological disease subtyping is carried out on the sample subjected to genomic testing (e.g. to prevent potential issues with second primary tumours, or tumour subtype evolution). At the very least, a histopathology report from a prior evaluation of the same specimen should be available.

Reason for testing and clinical context

Most laboratories carrying out NGS assays for clinical use have limited access to detailed medical histories of individual patients. Hence, genomic reports are often generated without knowledge that is relevant for best interpretation of the genomic findings, like the treatments received by the patient before the time of sample acquisition or the family history of cancer. These details, however, may be relevant for optimal interpretation of genomic biomarkers and their potential clinical relevance for an individual patient. Importantly, documenting whether the sample was obtained at a time of active disease progression holds particular significance in the context of liquid biopsy tests. Hence, we recommend fluent communication between physicians requesting the test and the laboratory carrying out the analysis to maximise the output of NGS reports in clinical samples, for example by providing relevant clinical context details to the laboratory as part of the test requisition form. This information should be also included in the NGS report to document the context available to the laboratory when reporting the results, similarly to how it is common practice in medical imaging reports.[12]

Recommendations

- Patient identification should be clear in the front page of the report and included in every page of the report. (Level A)
- Describe key biospecimen features clearly in the front page of the report, including histology, sample type, tissue preservation type (when applicable), date of acquisition, anatomical origin and source of matched normal DNA, when applicable. (Level A)
- Include key histopathological features of the sample under study (tumour type, histological subtype,

pathology-based estimation of tumour content) using standard classification systems. (Level A)
- Histopathological evaluation of the sample under study concurrent to genomic profiling is considered the preferred approach for optimal interpretation although relying on prior histopathology reports is acceptable particularly in the face of limited sample availability. (Level A)
- Indicate the 'reason for testing' and include any additional clinical context details provided to the laboratory. (Level B)

SECTION 2. ASSAY CHARACTERISTICS

Clinical genomic reports should identify the laboratory carrying out the test and mention the assay's name for clarity and reference, and provide a concise overview of the assay's capabilities, including whether it is based on tumour-only or paired tumour—normal material analysis. This initial brief description can be expanded in appendix sections of the report to include information on the covered genes and regions (for targeted panels) or genomic space (for whole-exome/genome sequencing), and the types of genomic alterations (e.g. gene variants, copy number changes and/or fusions), and other genomic measures beyond individual gene alterations (e.g. TMB, MSI, HRD, estimation of ploidy and/or viral integrations) that are tested. The bioinformatics methods used to process the NGS data should also be included, ideally referenced to pipeline repositories under version control. As previously mentioned, laboratories are subject to local or international standardisation principles that regulate in part how these details should be documented. Therefore, a reference should be provided pointing to the validation/accreditation process of the genomic test and laboratory carrying out the assay.

Furthermore, to allow expert readers to place the reported results into perspective, we recommend providing access to further details on the assay's key performance metrics as part of the appendix or through references to external documents. These include the sensitivity, specificity, accuracy and reproducibility for detection/quantification of the reported pieces of genomic information under relevant conditions, including (but not limited to) the type of material tested (e.g. FFPE, fresh frozen material, blood or other biospecimens), input DNA amount, sample collection and handling procedures, data processing and analysis protocols, variant allele frequency (VAF) thresholds used, other interpretation and reporting criteria, the instruments and reagents used in the assay, the qualifications of the laboratory personnel carrying out the test, and the quality control measures in place according to local or international standards and regulations. For liquid biopsies, it may include other parameters such as the original volume of plasma. The upfront section of the report should include a clear note in the event the study is being carried out under different conditions to those for which the assay has been validated.

Tumour-only targeted sequencing assays represent a particular scenario that is commonly used in clinical practice. These assays analyse tumour DNA without a matched germline control, and thus inaccuracies in, or inability to, determining the somatic versus germline origin of the observed variants could hinder the reliability of some of the results reported. Examples include the calculation of the TMB,[13,14] and the misattribution of clonal haematopoiesis events as somatic variant calls.[15,16] These limitations should be also clearly stated in the report, in line with the validation process undertaken for an assay.

Recommendations

- Identify the assay as well as the laboratory carrying out the test. Include a brief overview of the assay capabilities upfront, while a detailed description of the assay (tested genes/regions, alterations that the test has been validated for) can be included in later pages, appendix or referenced to external documents. (Level A)
- Provide the validation/accreditation status for the assay and laboratory upfront in the report. Assay performance metrics under relevant clinical conditions can be included in later pages, appendix or referenced to external documents. (Level A)
- If the assay is applied under different conditions to those where it was validated, a clear disclaimer should be reported stating how the assay reliability may be compromised. (Level A)
- For tumour-only assays, a caution note should be included for those measurements that may be affected by the limitations to determine the germline versus somatic origin of the variants. (Level A)

SECTION 3. SAMPLE-SPECIFIC ASSAY PERFORMANCE AND QUALITY CONTROLS

While the previous section refers to the general assay characteristics and would be mainly unchanged across different reports using that assay, a subsequent section should explain how the assay performed on the specific sample under study, compared to the minimal requirements for a reliable analysis. Reporting key quality metrics in a concise manner is essential to effectively document the quality of the genomic data generated for the analysed biospecimen. These metrics typically include quantitative and qualitative assessments of input DNA/RNA and median sequencing coverage; other parameters such as mapping rate can be provided as supplemental information.

In assays where a method for genomics-based calculation of tumour content has been validated, this information could be presented here to complement pathology-based estimation of tumour content in tissue biopsies. For cell-free DNA (cfDNA) liquid biopsy tests, the equivalent metric of tumour fraction or circulating tumour DNA

percentage (ctDNA%) should be reported in all instances as it is central to interpret the results.

The objective of providing these parameters is to instil confidence with respect to the accuracy of the specific results reported for the analysed biospecimen. To make the key information easily comprehensible, we recommend presenting it through qualitative assessments, where results are categorised (e.g. 'pass' or 'no pass') against established reference control values in the upfront part of the report. We recommend the incorporation of visual aids, such as colour-coded indicators or scales, to facilitate understanding whether the sample meets the quality control criteria for each of the analyses conducted (gene variants, copy number estimation, fusions and, when applicable, more complex genomic biomarkers), to easily identify any deviation from the optimal settings that may represent a limitation for interpreting the results of a particular test.

The extended section of the report can then delve into greater detail, offering insights into the test's sensitivity and specificity in assessing each type of alteration, and how the metrics for the biospecimen under examination relate to the optimal parameters for the assay to enable a comprehensive technical evaluation.

Recommendations

- We recommend using qualitative or semi-qualitative measures to describe the key quality metrics of the sample under study. (Level A)
- A comprehensive breakdown of quality metrics and how they relate to the assay's optimal standards can be provided in an annex. (Level A)
- If deviations in these metrics suggest that one or more specific analyses are non-evaluable (e.g. copy number estimation deemed unevaluable while variant calling remains evaluable), this should be clearly stated in the front page of the report to clearly differentiate the absence of biomarkers versus failed assessments. (Level A)
- In the case of liquid biopsy/cell-free DNA assays, an estimation of ctDNA% or tumour fraction should be reported as it is critical to contextualise the results. (Level A)
- The integration of visual aids in the report to represent quality metrics facilitates interpretation. (Level B)
- In tissue samples, genomics-based estimation of tumour purity can be included if the method for calculation has been validated, in addition to pathology-based tumour content estimation. (Level B)

SECTION 4. RESULTS

The report should contain an overview (e.g. in table format) of the genomic alterations detected in the sample. Some reports separate the descriptive list of results by alteration type (e.g. gene variants, copy number alterations [CNA] and fusions). Ideally, we recommend that genomic alterations would be ranked based on levels of clinical actionability to facilitate clinical interpretation and prioritisation of therapeutic options.

Each variant listed must be accompanied by a description that enables comprehension among clinical readers. This description should include details such as which gene is affected and the specific type of alteration detected, as well as an assessment of its functional/biological relevance, and, when pertinent, an evaluation of the level of evidence for clinical actionability. Point-by-point guidance on how to structure this description is provided below.

For consistency and clarity, we recommend the use of broadly adopted nomenclature schemes, such as those developed by the HUGO Gene Nomenclature Committee,[17] and the Human Genome Variation Society's mutation nomenclature[18] or the Ensembl genome database project.[19] The annex of the report could specify the used genome assembly (e.g. hg38) and the annotation schemes/nomenclatures as well as their versions. For all types of genomic alterations, it is recommended to specify the affected gene and the type of alteration detected.

For gene variants, the report should at least contain VAF, nucleotide sequence and/or cDNA change, effect class (missense, frameshift, nonsense, splice site, etc.) and, if the variant is protein-coding, the amino acid change, together with the gene transcript used for the variant mapping.

For fusions, we recommend reporting both fusion partners, the genomic breakpoints at the fusion junction, the assessment of the in-frame/out-frame status of the corresponding gene products and a metric for the relative amount of fusion present (e.g. total and percentage of fusion supporting reads or estimated copy number). Depending on the assay design, these findings can be based on DNA analysis or detected at the transcript level when concurrent RNA diagnostics is used.

For CNA, we advise reporting absolute gene copy number, although we acknowledge many targeted panels may not be able to accurately compute absolute copy number; in that case, a categorical classification would suffice. In either case, the criteria to define CNAs should be documented. Caution should be used when reporting low-level amplifications or single-copy deletions, to avoid overinterpretation of their clinical relevance.

Additional information such as the description of the gene(s) as an oncogene or tumour suppressor (relevant for all alteration types), or whether a variant occurred at a mutation hotspot could facilitate interpretation.

Depending on the assay's capabilities, it may be possible to estimate (sub)clonality of the gene variants and loss of heterozygosity of a gene harbouring a variant. It is important to acknowledge that clonality assessment of biomarkers is complex and not yet part of clinical guidelines; however, the potential relevance of the variant clonality seems clear from a biological perspective and, if the assay is robustly validated for this assessment, reporting of the clonality of biomarkers could therefore be considered.[20] Similarly, the bi-allelic inactivation status of tumour

suppressor gene (TSG)-based biomarkers (such as *BRCA1/2* inactivation for PARP inhibitors) is not a defined criterion in current clinical guidelines; however, for many TSGs, bi-allelic inactivation is essential for their biological effect (the classical two-hit model[21]) and reporting the bi-allelic genomic status of TSGs could therefore be considered. Of note, the interpretation of this assessment is complex: while the TSG may be inactivated via two different gene alterations in each respective allele, a fraction of suspected monoallelic genomic alterations may be associated with complete TSG inactivation via means that are missed by clinically used assays, such as single-copy losses, copy-neutral loss of heterozygosity, complex rearrangements or other non-genomic mechanisms. Hence, if the assay has been validated for these measurements, we recommend including them as additional information for expert interpretation, but these should (for now) not be considered for ranking of clinical actionability.

Recommendations

- The report should contain a detailed description of the identified genomic alterations, with description of the gene name and type of alteration. (Level A)
- For gene variants, the effect, sequence and/or cDNA change and—when appropriate—amino acid change should be reported together with the gene transcript used for the genomic mapping. (Level A)
- For fusions, we recommend reporting both fusion partners, quantification metrics, the genomic breakpoints at the fusion junction and the in-frame/out-frame status. (Level A)
- Copy number alterations can be reported categorically (Level A) or, if the assay permits, as total estimated number of copies. (Level B)
- We recommend the use of broadly adopted gene and gene alteration nomenclatures, which should be specified in the appendix of the report. (Level A)
- Additional details like the role of the affected gene (tumour suppressor versus oncogene) and whether a variant occurs in a recurrent hotspot can be added to provide further information. (Level B)
- VAF values should be reported for gene variants. (Level A)
- Bi-allelic alteration status and (sub)clonality can be reported but we recommend caution when interpreting clinical impact. (Level B)

Annotation of biological/functional impact and clinical relevance of a variant

The report should include a biological/functional interpretation of each detected variant (i.e. whether it is likely to affect the function of the encoded protein). This annotation is necessary to avoid overinterpretation of passenger and/or benign genomic alterations.

The most used classification scheme for functional relevance is based on a five-tier system classifying variants as: benign, likely benign, variant of unknown significance (VUS), likely pathogenic or pathogenic.[5] However, this system was originally designed for classifying germline variants, and other schemes have been later developed to classify somatic genomic alterations in cancer, such as the one proposed by the 'ClinGen/CGC/VICC' group.[6] These and other similar classification systems are based on variant effects that are known or can be presumed, as well as on *in silico* prediction tools. While a review of the different variant functional classification options is outside the scope of this work, the panel recommends adhering to a well-recognised framework, being consistent in the use of terminology, and providing a reference to the system used in the report.

For CNA and other structural variants, we acknowledge that similar guidelines for functional impact annotation are largely missing. In general terms, we recommend to only report as functionally relevant copy gains/amplifications for oncogenes and copy losses for tumour suppressor genes, whereas functional annotation of fusions should be evaluated on a case-by-case basis.

Only those alterations with an expected impact on the gene function (pathogenic or likely pathogenic, or equivalent terminology) should be included in the main report and evaluated for clinical actionability. We recommend that 'likely benign' and 'benign' (or equivalent terminology) genomic alterations are not included in the report. If VUS (or equivalent terminology) are included in the report, they should be clearly labelled and/or listed in a separate section to avoid overinterpretation of findings.

Annotation of clinical actionability

Annotation of the potential clinical actionability of the genomic alterations is a process separate from the assessment of their biological/functional impact, in which the possible therapeutic, diagnostic or prognostic implications of a given alteration are described. This process should be based on up-to-date evidence. Clinical actionability annotation is a challenging task; however, this information can facilitate the clinical review of the NGS results, and it is thus an important part of the report. Ensuring harmonisation and implementation of this process according to the highest standards is crucial to minimise the risk of misinterpretation of data that can be relevant for therapeutic decisions.

A given alteration can be assigned to different levels of clinical actionability for different therapeutic interventions. Furthermore, the same alteration may have different levels of clinical actionability in different malignancies or clinical settings. It is critical to distinguish between on-tumour evidence (clinical actionability demonstrated in the same tumour type) and off-tumour evidence (clinical actionability in other malignancies). In addition, the nature of the match between the genomic alteration and the corresponding biomarker should be also detailed in the report, i.e. indicating whether it is based on the presence of a specific event [e.g. epidermal growth factor receptor (*EGFR* T790M alteration)], a certain broader genomic description (e.g. *EGFR* exon 20 insertion) or a functional term (e.g. activating

EGFR variant). The report should also reference the knowledge base (at minimum) and/or (ideally) the publication underlying the classification of the alteration's actionability. Indeed, compressing these multiple lines of evidence concisely within a report represents a challenge towards maintaining comprehension of the results for the individual case under study.

We recommend that genomic reports rank the actionability of the (likely) pathogenic genomic alterations using scales or frameworks that consider clinical evidence and the magnitude of benefit derived from a therapeutic intervention. This approach, rather than using a binary classification as 'actionable' or 'not actionable', would aid patients and physicians in prioritising therapeutic options. Notable examples of such frameworks include the ESMO's Scale for Clinical Actionability of molecular Targets (ESCAT),[8] the OncoKB classification system[22] or the Association for Molecular Pathology/American Society of Clinical Oncology/College of American Pathologists joint Consensus Recommendation,[7] but many other examples exist in the literature.[23,24] Also, it should be acknowledged that these classification systems may not rank other forms of clinical value (i.e. for diagnostic or prognostic biomarkers), as some of these systems were primarily designed to rank direct biomarker—drug treatment matches. To assist in genomic clinical actionability annotation, several knowledge bases are available, including OncoKB,[22] JAX-CKB[25] and CIViC,[26] among others. These knowledge bases are important towards standardised clinical actionability interpretation.

For those reports including clinical actionability assessment, it is advised to sort the actionable genomic events based on the level of evidence, from higher to lower. For biomarkers matching approved drugs for the tumour type under study, we recommend that the reports specifically name these drugs, keeping in mind the caveats mentioned above. In cases where actionable biomarkers match experimental drugs, or drugs that are not approved for the tumour type under study, these limitations should be clearly reported. For lower tiers of clinical actionability (e.g. investigational treatment indications) it is sufficient, in general, to report drug types or mechanisms of action (e.g. PARP inhibitors, EGFR-tyrosine kinase inhibitors, EGFR blocking antibodies) rather than specific drug names. To maintain conciseness, biomarkers could be excluded from the report when only pre-clinical evidence is available.

It is paramount that physicians and other recipients of the report understand that the annotation of the potential clinical actionability of alterations cannot be taken as a clinical recommendation, but as a tool to facilitate the incorporation of genomic data into the complex treatment decision-making process. Treatment decisions should always stem from a deep understanding of the clinical case by the treating physician(s), ideally with support from multidisciplinary (molecular) tumour boards, as the clinical context dictates the implications of a given actionable biomarker. For those genomic reports listing potentially matching drugs, it should acknowledge that clinical decisions and treatment indications require a holistic view of the patient's medical history and clinical status, and not just the detection of a predictive biomarker.

Clinical trial matching in genomic reports

Genomic alterations detected in clinical NGS tests can be actionable by means of drugs under evaluation in clinical trials. The panel acknowledges the value of clinical trials in providing early access to potentially beneficial agents to patients with advanced cancers; genomic reports could play an important role by alerting the treating physician for investigational opportunities tailored to biomarker-defined populations. However, several points need to be considered regarding including clinical trial options as part of the clinical actionability annotation. Firstly, clinical trial inclusion criteria go beyond the presence of a given biomarker, and it is largely defined by different clinical variables and patient preferences that are not captured by genomic tests. Secondly, clinical trials are usually only conducted at selected centres. Moreover, patients may have clinical trial options irrespective of genomic criteria, so the trials suggested in an NGS report may not represent the entire scope of trial opportunities. Lastly, with some local exceptions, very few resources to facilitate clinical trial matching are available[27]; public sources of information are Clinicaltrial.gov (US-based) or EudraCT (European, country-tailored), but their data models are not designed to accommodate an accurate interrogation of the genomics-based inclusion criteria.

We recommend that potential clinical trial matches are only annotated in the NGS reports if a reliable and up-to-date database of genomic biomarker-driven trials specific for the patient's disease and country/region is available, and being aware that it is the responsibility of the treating physician to further evaluate the suitability of the patient to those (or other) trial opportunities.

Recommendations

- Genomic alterations should be reported in accordance with a standardised terminology for functional/biological impact. (Level A)
- We recommend focussing on (likely) pathogenic (or equivalent nomenclature) genomic alterations in the main results section of the report. VUS can be included, but they should be clearly labelled or reported in a separate section to avoid overinterpretation. (Level A)
- Only (likely) pathogenic/oncogenic driver alterations should be evaluated for clinical actionability. VUS and (likely) benign variants should not be considered when assessing clinical actionability. (Level A)
- Reported biomarkers should be ranked following standardised levels of clinical actionability. (Level A)
- Evidence supporting the (level of) actionability of a given biomarker should be documented for reference. (Level A)
- For brevity, biomarkers with only pre-clinical evidence suggesting potential actionability can be omitted from the report or listed separately. (Level B)

- When a variant has high clinical actionability with an approved therapeutic, the name of the drug should be included. (Level B)
- We recommend clinical trial matching to be included in the report, but always contingent on access to a comprehensive and up-to-date clinical trial database that is relevant for the region of the patient being tested. (Level B)
- Overall, reports should emphasise that the clinical actionability annotation cannot be considered as a treatment recommendation, but as a tool to facilitate the clinical review of the NGS results. (Level A)

Reporting genomic biomarkers beyond individual genes

Genomic biomarkers derived from measures that go beyond events affecting individual genes are increasingly being adopted in clinical practice for guiding treatment selection. Examples include the use of the TMB or MSI status to guide immune checkpoint blockade treatment, or the identification of HRD to guide treatment with PARP inhibitors or platinum-based chemotherapeutics. Other mutational signatures, such as those indicative of tobacco- or UV-based mutagenesis, as well as information about potential viral integrations in cancer genomes, can have clinical value for informing clinicians about the potential tissue of origin for cancers of unknown primary (CUP)[28] but have not yet been validated for clinical decision making. While these biomarkers were mostly derived originally from WES or WGS datasets, some targeted panels commonly used in clinical practice are incorporating equivalent measures. When reporting continuous biomarkers such as mutational signatures, we recommend displaying the biomarker's potential range and, if relevant, the (assay-specific) validated threshold for clinical actionability; graphical solutions can aid presenting the sample's position within the biomarker range, thereby facilitating intuitive interpretation.

For clarity and generalisability, we recommend providing an annex (or reference to external documents) stating how these measures were calculated, the genomic space that was considered, in which units the measurements are being reported, and including the justification on the thresholds used to classify the results when appropriate.

Recommendations

- We recommend including genomic biomarkers derived from measures beyond individual genes, like TMB, MSI, HRD, other mutational signatures and viral integrations in clinical reports when the assay has been validated for that purpose. (Level A)
- The same principles of evidence for clinical actionability assessment also apply to signatures/biomarkers that go beyond individual genes. (Level A)
- For continuous biomarkers, we recommend presenting results graphically for intuitive interpretation, showing the population range, clinically relevant threshold and sample position within that range. (Level B)
- Information on the methodology for their calculation, measurement units, threshold determination and considered genomic space should be included in the appendix of the report or through reference to external documents. (Level A)

Identification of variants with potential implication for hereditary cancer

Treating physicians should be assisted in identifying patients who may benefit from consultation with clinical geneticists and other genetics counsellors. To that end, we recommend that variants that may require follow-up confirmatory germline testing are clearly marked in the report. We stress the need to discuss potential implications of germline testing with the patient before obtaining informed consent for germline testing. Written patient information provided ahead of tumour sequencing analysis should mention potential for the analysis to identify genetic changes that might inform on risk of future cancers and/or be heritable through the family. The information provided should reassure the patient that they will receive additional information, consultation and request for explicit consent ahead of further analyses which would confirm such a variant as germline.

For assays based on matched tumour-germline sequencing, the germline origin of any variant could be determined with certainty. In that case, we recommend including the germline versus somatic origin of alterations in the NGS report (if the patient consented for this). However, many NGS tests used in clinical practice are based on tumour-only sequencing, in which assessing the somatic versus germline origin of a variant may be challenging; the likelihood that a tumour-observed variant is of germline origin varies by gene and according to the observed VAF. We recommend adhering to the recently published ESMO PMWG recommendations for flagging potentially germline variants from tumour-only data and recommending follow-up germline-focused analysis.[29]

The increasing incorporation of WES and WGS assays into clinical practice underscores the relevance for identification, reporting and management of non-cancer-related secondary findings. To that end, specific recommendations, such as those established by the American College of Medical Genetics and Genomics, are available for guidance.[30]

Recommendations

- For all sequencing platforms based on matched tumour—normal sample sequencing, relevant (likely) pathogenic germline variants in cancer predisposition genes should be prominently marked for follow-up at a specialised clinical genetics department. (Level A)
- For tumour-only sequencing, we recommend adhering to ESMO PMWG 2023 recommendations for guidance on identifying individuals who may benefit from

referral to cancer genetics specialists for consideration of follow-up germline testing. (Level A)

SECTION 5. SUMMARY OF RELEVANT EVENTS AND INTERPRETATION

The front page of a genomic report designed for clinical use should feature a succinct, yet comprehensive, summary of the most relevant findings of the NGS assay. This summary should offer physicians a quick overview of the key results for clinical interpretation and, if possible, specifically answer the clinical question of the physician requesting the test. This summary must contain information on the genomic alterations and (potential) germline variants that are clinically relevant (if any). This text can also elaborate on complex issues integrating all findings, such as the potential importance of co-occurring genomic alterations in the sample under study, the significance of the results considering the pathology and clinical information provided to the NGS laboratory, or addressing any uncertainties that may necessitate follow-up confirmatory or complementary tests. We recommend presenting this summary in a narrative manner, using a language that facilitates comprehension by physicians who may not be experts in genomics.[31]

Yet, the panel recognises that the ultimate clinical interpretation of genomic findings needs to be guided by the treating physician in the context of all the information on the individual patient's medical history and preferences. This underscores the need for multidisciplinary teams of experts, such as those participating in molecular tumour boards, who can assist physicians in interpreting clinical relevance of genomic findings in a consistent manner. Conclusions of this expert discussion should be also documented to complement the NGS report in the patient medical notes.

Recommendations

- Clinical genomic reports should include a summary of the most relevant findings to facilitate the interpretation process. (Level A)
- A table/list with a simplified summary of clinically relevant findings can be included to facilitate comprehension. (Level B)
- It is desirable for clinical genomic report to include a narrative summary that provides a comprehensive, integrated interpretation of all findings and potential limitations, including recommendation for follow-up or confirmatory tests when appropriate. (Level B)
- When clinical interpretation occurs in the context of a molecular tumour board meeting, we recommend documenting the conclusions to complement the NGS report in the patient medical notes. (Level B)

CLOSING REMARKS AND PERSPECTIVES

The application of genomics to clinical care is a flourishing yet imperfect field, characterised by rapidly evolving knowledge driven by emerging data and new technological capabilities. Over the last decade, we have witnessed significant advances in both the generation and analysis of sequencing data. However, the translation of these advances into routine clinical management of patients with cancer necessitates the coupling of such progress with the appropriate provision of resources and expertise within our health care systems, including diagnostic laboratories, education of health care professionals and building multidisciplinary teams to support the optimal integration of these data into treatment recommendations. Moreover, in-system consolidation of genomic testing as a medical procedure and part of the patient pathway is imperative, akin to other diagnostic tests routinely used in oncology.

At present, one of the most pressing challenges for effectively reducing uncertainties around clinical relevance of genomic alterations relates to limitations of the databases for clinical actionability mapping. The lack of a comprehensive, open-source knowledge base of clinical actionability which is constantly up to date with European and/or local clinical guidelines seriously complicates automated clinical actionability mapping for patients. This makes it more challenging to ensure optimal variant interpretation, while seriously increasing the workload of manual review for clinical experts. Furthermore, with some local exceptions, there is a lack of informatics-friendly databases with structured data on (genomic) inclusion criteria for clinical trials in oncology, which limits the feasibility of automated clinical trial matching in clinical genomic reports, thereby limiting important regional inequalities in cancer care. With the ever-increasing employment of broad genomic testing in oncology, serious investments are needed to cover these essential pieces of infrastructure, to ensure the optimal employment of genomics-based precision oncology in the upcoming decades.

The integration of interactive reports and dynamic visualisation tools into electronic patient records also represents a major hurdle for clinical informatics in the coming years; this will require significant efforts and alignment with relevant data management regulations, such as the European Health Data Space initiative. Another challenge emerges from the possibilities for longitudinal monitoring of cancer evolution through liquid biopsy tests, which require integrating results from prior tests, or the room for re-evaluation of findings as new clinical data emerge.

In addition, we note that facilitating patient comprehension and effective communication of genomic data, along with their clinical implications, represents a notable barrier to empowering patients to participate in therapeutic decisions.[32,33] Tailoring reports explicitly to enhance patient understanding, whether as a separate/standalone document or as an integrated section within comprehensive genomic reports, is crucial for achieving the goals of precision medicine.

With the increasing number of genomics-based biomarkers and the anticipated surge in clinical adoption of WES and WGS, the interpretation of genomic results is becoming more complex, and we foresee that the importance of user-friendly and well-annotated reporting will continue to grow to ensure optimal patient benefit. Genomics will also be increasingly integrated with other emerging, complementary

types of diagnostics, including digital pathology, methylation, transcriptomics and protein testing. As a result, clinical experts will require more advanced patient reports, which we expect will increasingly embed interactivity and data visualisation tools.[34,35] It is evident that effective integration of complex multi-omics biomarkers into clinical decision making will depend on more sophisticated decision-support tools. Anticipating this demand, the development of artificial intelligence methods to harness multi-omics biomarkers is expected to play a key role in advancing clinical implementation of precision medicine, significantly influencing how molecular profiling data are reported and communicated to both physicians and patients.

While these recommendations focus on implementation of genomic report into routine clinical practice, we acknowledge the importance of large, clinically annotated, genomic data repositories for advancing the field of precision medicine. For that, large-scale (international) data sharing will be key, and thus alignment of data reporting and sharing efforts are needed. Notable examples on how to optimise data collection for accelerating research include, for example, the recent proposal for a minimal dataset for cancer from the 1+Million Genomes project.[36]

In sum, genomic reports represent the output of a complex process that transforms genomic information into a format suited for assisting clinical decision making. We believe that the present recommendations can help making genomic reports more informative for physicians. As for any other medical procedure, effective communication among all stakeholders involved in patient care is paramount to maximise the positive impact of genomic testing on patient outcomes. When possible, sequencing laboratories can adapt part of the content of their reports, particularly clinical actionability annotation, in order to accommodate specific needs of the medical teams that receive that information. Therefore, we advocate close collaboration between medical, biological and technical experts (among others, pathologists, cancer genomics experts, molecular biologists, geneticists and bioinformaticians) responsible for conducting and interpreting genomic tests to minimise uncertainties regarding genomic results. To that end, the establishment of cancer genomics expertise as part of multidisciplinary care teams, sometimes in the form of molecular tumour boards, represents an opportunity to standardise the clinical interpretation of genomic data based on up-to-date evidence and promote equitable access to the potential of precision medicine.

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DISCLOSURE

FA reports receipt of a fee to institution for participation in advisory board from AstraZeneca, Boston Pharmaceutics, Daiichi Sankyo, Gilead, Guardant Health, Eli Lilly, N-Power Medicine, Novartis, Owkin, Pfizer, Roche, Servier; receipt of a personal fee for participation in advisory board from Lilly France; receipt of research grants to institution from AstraZeneca, Daiichi Sankyo, Guardant Health, Ely Lilly, Novartis, Owkin, Pfizer, Roche. JB reports receipt of a fee as an invited speaker from AstraZeneca; receipt of a fee to institution for educational programmes from AstraZeneca, MSD; receipt of a fee to institution as a Steering Committee Member from AstraZeneca; receipt of a fee to institution as a local principal investigator from MedSir. EC reports receipt of a fee for participation in advisory board from Astellas, AstraZeneca, Bayer, Daiichi Sankyo, Janssen, Eli Lilly, Medscape, MSD, Novartis, Pfizer; receipt of a fee as an invited speaker from Astellas, AstraZeneca, Clovis, Janssen, Medscape, Pfizer; receipt of funding to institution from AstraZeneca; receipt of research grants to institution from Bayer, Janssen, Pfizer; receipt of a fee to institution as a local principal investigator from Janssen, MSD, Pfizer. GC reports receipt of a fee for participation in advisory board from AstraZeneca, BMS, Celcuity, Daiichi Sankyo, Exact Sciences, Gilead, Eli Lilly, Menarini, Merck, Pfizer, Roche, Veracyte, Ellipsis; receipt of a fee as an invited speaker from AstraZeneca, Daiichi Sankyo, Novartis, Pfizer, Roche; receipt of a fee for writing engagement from Pfizer; receipt of funding to institution for running phase I studies from Astellas, AstraZeneca, Blueprint Medicine, BMS, Daiichi Sankyo, Kymab, Novartis, Phylogen, Roche, Sanofi; receipt of a research grant to institution for running an investigator initiated trial from Merck; receipt of a fee to institution as a coordinating principal investigator from Relay Therapeutics; non-financial interest for advisory role as an officer in Consiglio Superiore di Sanità, Italian National Health Council as an Advisor for Ministry of Health, in Europa Donna as a Member of the Scientific Council, in EUSOMA as a Member of the Advisory Council, in Fondazione Beretta; non-financial interest for a leadership role in ESMO, Lega Italiana Lotta ai Tumori as a Member of Board of Directors. AMC reports receipt of a fee as an invited speaker from BMS, MSD, Novartis, Pierre Fabre. RD reports receipt of a fee for participation in advisory board from Foundation Medicine, Roche; receipt of a fee as an invited speaker from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Ipsen, Janssen, Libbs, Eli Lilly, Merck Sharp & Dohme, Roche, Sanofi, Servier, Takeda; part time employment in Oncoclinicas; owning stocks/shares in Trialing; receipt of a research grant from Merck; receipt of research grants to institution from AstraZeneca, Daiichi Sankyo, GlaxoSmithKline, Novartis. PH reports receipt of a fee for participation in advisory board from Platomics; receipt of a fee as an invited speaker from Roche, Trillium. AI reports receipt of a fee for participation in advisory board from Bayer, Chugai Pharmaceutical Co., Ltd., GSK, Philips, Roche; non-financial interest to institution as a coordinating principal investigator from AstraZeneca, Bayer, Ipsen, Merck, MSD, Roche. CM reports

receipt of a fee for participation in advisory board from AstraZeneca, Bayer, Daiichi Sankyo, Roche; receipt of a fee as an invited speaker from Veracyte and Illumina. KM reports receipt of a fee to institution for participation in advisory board from AbbVie, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Eli Lilly, Merck, MSD, Pfizer, Roche; non-financial interest as a coordinating principal investigator from AstraZeneca; non-financial interest from receiving the product samples from Roche SS. HEGR reports receipt of a fee to institution as an invited speaker from Illumina; receipt of a fee to institution for participation in round table from Incyte; receipt of a fee to institution for participation in debate from Merck; receipt of a fee to institution for providing an expert testimony from Novartis; non-financial interest as a coordinating principal investigator from funding to institution by Illumina, Roche Norway; non-financial interest as a coordinating principal investigator from institutional collaboration with Oxford Nanopore; non-financial interest from a leadership role in National Competence Network for Precision Medicine, National Infrastructure for Precision Diagnostics (InPreD), The Norwegian Association of Pathology, The Norwegian Association for Molecular Pathology. TS reports receipt of a fee for participation in patient advisory board from MSD; receipt of a fee for participation in advisory board from Roche; receipt of a fee as an invited speaker from Pfizer, Roche. CT reports receipt of a fee for participation in advisory board from Roche; receipt of a fee as an invited speaker from AstraZeneca. EVA reports receipt of a fee for participation in advisory board from Enara Bio, Genome Medical, Genomic Life, Manifold Bio, Monte Rosa Therapeutics, Riva Therapeutics, Serinus Bio; receipt of a fee for providing consultancy from Janssen, Tango Therapeutics; receipt of research grants to institution from BMS, Novartis; owning stocks/shares in Enara Bio, Genome Medical, Genomic Life, Manifold Bio, Microsoft, Monte Rosa Therapeutics, Riva Therapeutics, Serinus Bio, Syapse, Tango Therapeutics. CBW reports receipt of a fee for participation in advisory board from BMS, Celgene, Rafael, RedHill, Roche, Shire/Baxalta; receipt of a fee as an invited speaker from Amgen, AstraZeneca, Bayer, BMS, Celgene, Chugai, Falk, GSK, Janssen, Merck, MSD, Roche, Servier, Sirtex, Taiho; receipt of a fee for an expert testimony from Janssen; receipt of travel support from Bayer, Celgene, RedHill, Roche, Servier, Taiho; non-financial interest for receipt of research grant both personal and to institution from Roche; non-financial interest for serving as an officer in AIO—Arbeitsgemeinschaft Internistische Onkologie (Germany); non-financial interest for advisory role in EU Commission—DG RTD as a member of the EU Commission Mission Board for Cancer. DT reports receipt of funding to institution for participating in basket trials from Roche, Taiho Oncology, Janssen; owning stocks/shares in Roche. JM reports receipt of a fee for participation in advisory board from Amgen, Amunix Pharmaceuticals, AstraZeneca, Janssen, Pfizer, Roche; receipt of a fee to institution for participation in advisory board from Nuage Therapeutics; receipt of a fee as an invited speaker from AstraZeneca, GuardantHealth, MSD; receipt of research grants to institution from Amgen, AstraZeneca, Pfizer Oncology; non-financial interest from receiving product samples for access to drugs in early development for pre-clinical testing from AstraZeneca. All other authors have declared no conflicts of interest.

REFERENCES

1. Schilsky RL, Longo DL. Closing the gap in cancer genomic testing. *N Engl J Med*. 2022;387(23):2107-2110.
2. Mosele F, Remon J, Mateo J, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. *Ann Oncol*. 2020;31(11):1491-1505.
3. De Moor JS, Gray SW, Mitchell SA, et al. Oncologist confidence in genomic testing and implications for using multimarker tumor panel tests in practice. *JCO Precis Oncol*. 2020;4:620-631.
4. Bayle A, Bonastre J, Chaltiel D, et al. ESMO study on the availability of biomolecular technologies in oncology in Europe. *Ann Oncol*. 2023;34(10):934-945.
5. Richards S, Aziz N, Bale S, et al., ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424.
6. Horak P, Griffith M, Danos AM, et al. Standards for the classification of pathogenicity of somatic variants in cancer (oncogenicity): joint recommendations of Clinical Genome Resource (ClinGen), Cancer Genomics Consortium (CGC), and Variant Interpretation for Cancer Consortium (VICC). *Genet Med*. 2022;24(5):986-998.
7. Li MM, Datto M, Duncavage EJ, et al. Standards and guidelines for the interpretation and reporting of sequence variants in cancer: a joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. *J Mol Diagn*. 2017;19(1):4-23.
8. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann of Oncol*. 2018;29(9):1895-1902.
9. Tamborero D, Dienstmann R, Rachid MH, et al. Support systems to guide clinical decision-making in precision oncology: the Cancer Core Europe Molecular Tumor Board Portal. *Nat Med*. 2020;26(7):992-994.
10. Reardon B, Moore ND, Moore NS, et al. Integrating molecular profiles into clinical frameworks through the Molecular Oncology Almanac to prospectively guide precision oncology. *Nat Cancer*. 2021;2:1102-1112.
11. Schmid S, Jochum W, Padberg B, et al. How to read a next-generation sequencing report—what oncologists need to know. *ESMO Open*. 2022;7(5):100570.
12. Loy CT, Irwig L. Accuracy of diagnostic tests read with and without clinical information: a systematic review. *JAMA*. 2004;292(13):1602-1609.
13. Asmann YW, Parikh K, Bergsagel PL, et al. Inflation of tumor mutation burden by tumor-only sequencing in under-represented groups. *NPJ Precis Oncol*. 2021;5(1):22.
14. Nassar AH, Adib E, Alaiwi SA, et al. Ancestry-driven recalibration of tumor mutational burden and disparate clinical outcomes in response to immune checkpoint inhibitors. *Cancer Cell*. 2022;40(10):1161-1172.e5.
15. Jensen K, Konnick EQ, Schweizer MT, et al. Association of clonal hematopoiesis in DNA repair genes with prostate cancer plasma cell-free DNA testing interference. *JAMA Oncol*. 2021;7(1):107-110.
16. Marchall CH, Gondek LP, Luo J, Antonarakis ES. Clonal hematopoiesis of indeterminate potential in patients with solid tumor malignancies. *Cancer Res*. 2022;82(22):4107-4113.
17. Bruford EA, Braschi B, Denny P, et al. Guidelines for human gene nomenclature. *Nat Genet*. 2020;52(8):754-758.
18. den Dunnen JT, Antonarakis SE. Mutation nomenclature extensions and suggestions to describe complex mutations: a discussion. *Hum Mutat*. 2000;15(1):7-12.
19. Martin FJ, Amode MR, Aneja A, et al. Ensembl 2023. *Nucleic Acids Res*. 2023;51(D1):D933-D941.

20. Boscolo Bielo L, Trapani D, Repetto M, et al. Variant allele frequency: a decision-making tool in precision oncology? *Trends Cancer*. 2023;9(12):1058-1068.
21. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A*. 1971;68(4):820-823.
22. Chakravarty D, Gao J, Phillips SM, et al. OncoKB: a precision oncology knowledge base. *JCO Precis Oncol*. 2017;2017:PO.17.00011.
23. Leichsenring J, Horak P, Kreutzfeldt S, et al. Variant classification in precision oncology. *Int J Cancer*. 2019;145(11):2996-3010.
24. Lin FP, Thavaneswaran S, Grady JP, et al. Criteria-based curation of a therapy-focused compendium to support treatment recommendations in precision oncology. *NPJ Precis Oncol*. 2021;5:58.
25. Patterson SE, Liu R, Statz CM, et al. The clinical trial landscape in oncology and connectivity of somatic mutational profiles to targeted therapies. *Hum Genomics*. 2016;10:4.
26. Griffith M, Speis NC, Krysiak K, et al. CIViC is a community knowledgebase for expert crowdsourcing the clinical interpretation of variants in cancer. *Nat Genet*. 2017;49(2):170-174.
27. Klein H, Mazor T, Siegel E, et al. MatchMiner: an open-source platform for cancer precision medicine. *NPJ Precis Oncol*. 2022;6(1):69.
28. Schipper LJ, Samsom KG, Snaebjornsson P, et al. Complete genomic characterization in patients with cancer of unknown primary origin in routine diagnostics. *ESMO Open*. 2022;7(6):100611.
29. Kuzbari Z, Bandlamudi C, Loveday C, et al. Germline-focused analysis of tumour-detected variants in 49,264 cancer patients: ESMO Precision Medicine Working Group recommendations. *Ann Oncol*. 2023;34(3):215-227.
30. Miller DT, Lee K, Abul-Husn NS, et al. ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2023;25(8):100866.
31. Martin NA, Tepper JE, Giri VN, et al. Adopting consensus terms for testing in precision medicine. *JCO Precis Oncol*. 2021;5:PO.21.00027.
32. Solomon I, McGraw S, Shen J, et al. Engaging patients in precision oncology: development and usability of a web-based patient-facing genomic sequencing report. *JCO Precis Oncol*. 2020;4:307-318.
33. Blanchette PS, Spreafico A, Miller FA, et al. Genomic testing in cancer: patient knowledge, attitudes, and expectations. *Cancer*. 2014;120(19):3066-3073.
34. Gray SW, Gagan J, Ceremi E, et al. Interactive or static reports to guide clinical interpretation of cancer genomics. *JAMIA*. 2018;25(5):459-464.
35. Tamborero D, Dienstmann R, Rachid MH, et al. The molecular tumor board portal supports clinical decisions and automated reporting for precision oncology. *Nat Cancer*. 2022;3(2):251-261.
36. Riba M, Sala C, Culhane AC, et al. The 1+million genomes minimal dataset for cancer. *Nat Genet*. 2024;56:733-736.