Panels, exomes or genomes? A critical appraisal of whole genome sequencing as a routine test in cancer diagnostics

Abstract

Cancer genomic profiling requires a choice between targeted gene panels, whole exome sequencing and whole genome sequencing (WGS). This narrative review appraises WGS as a routine diagnostic test from the pathologist's perspective, with attention to resource-limited health systems. WGS detects small variants, copy number changes, structural variants and mutational signatures in one DNA assay, and programmes in England and the Netherlands show it can be delivered routinely. The same programmes define its limits. In the Dutch WIDE study, WGS failed in 30% of samples, mainly because of low tumour purity, and only 147 of 603 patients with actionable biomarkers started matched therapy; in English paediatric practice, management was unchanged in about 93% of cases. Expressed fusions need RNA confirmation, and low-frequency variants are better detected by deep panels. We found no randomised trial comparing WGS with panel testing, and cost-effectiveness modelling in lung cancer does not favour it. The NHS England National Genomic Test Directory and European Society for Medical Oncology recommendations already limit WGS, or broad sequencing, to defined indications. We propose a five-step, three-tier extension, not yet validated, in which test choice depends on access to matched therapy, indication, specimen and laboratory capability, and each WGS indication has a targeted comparator. In health systems such as India's, where pathology relies on formalin-fixed tissue, testing is largely paid for out of pocket and many patients with a targetable driver go untreated, validated panels, with hub referral of paediatric, acute leukaemia and sarcoma cases for WGS, are a defensible standard.

Keywords: whole genome sequencing; molecular pathology; high-throughput nucleotide sequencing; precision medicine; developing countries

Introduction

Next-generation sequencing (NGS) has moved cancer classification from purely histopathological frameworks towards molecularly defined entities.[1] Three approaches are used clinically (table 1): targeted gene panels, whole exome sequencing (WES) and whole genome sequencing (WGS).[2]

Reviews of WGS in oncology have largely come from the centres that deliver it,[3] within health systems that have already decided where to use it. NHS England commissions WGS for defined cancer indications,[4] and the European Society for Medical Oncology (ESMO) specifies the tumour types in which broad sequencing is justified.[5,6] These frameworks do not address how a pathology service without fresh-frozen tissue pathways, an accredited genome laboratory or reimbursed targeted drugs should choose a test. That is the position of many laboratories in low- and middle-income countries, including India.

This review therefore has three aims: to compare the three approaches briefly; to appraise the evidence from routine WGS programmes, including their failures, from the pathologist's perspective; and to propose an indication-led, capability-tiered model for test selection, set out as a table of recommendations (table 2) and a five-step decision algorithm (figure 1).

We searched PubMed for English-language articles published up to 11 November 2026 using combinations of the terms “whole genome sequencing”, “whole exome sequencing”, “targeted gene panel”, “comprehensive genomic profiling”, “cancer diagnosis”, “clinical implementation”, “cost” and “India”. We prioritised guidelines, randomised trials, prospective implementation studies, micro-costing studies and large real-world cohorts, and identified further sources from reference lists; 77 sources are cited. As this is a narrative review, we applied no formal inclusion criteria and did not assess risk of bias.

Sequencing approaches in brief

Targeted panels range from amplicon hotspot assays to hybrid-capture comprehensive genomic profiling (CGP) panels of several hundred genes. Deep sequencing gives detection limits of about 2–5% variant allele frequency, and hybrid-capture panels also detect copy number variants (CNVs) and structural rearrangements[7,8] and report tumour mutational burden (TMB).[9] Panels are hypothesis-driven: drivers

outside the targeted regions, deep intronic variants and rearrangements with unanticipated breakpoints are missed.

WES captures the exons of about 20,000 genes, roughly 1–2% of the genome.[10] It is usually performed on matched tumour–normal pairs to remove germline polymorphisms[11] and is the reference against which panel-derived TMB has been validated,[9] but it detects structural variants (SVs) poorly because most breakpoints are non-coding.[12] As panels have grown and WGS costs have fallen, its clinical niche has narrowed.

WGS sequences the genome without enrichment and detects single nucleotide variants (SNVs), small insertions and deletions (indels), CNVs and SVs in one DNA assay, together with non-coding drivers such as *TERT* promoter mutations and genome-wide mutational signatures.[12,13] Two qualifications matter for what follows. Clinical tumour WGS is sequenced at about 90–100×,[14,15] well below the depth of targeted panels,[7] and detecting a rearrangement in DNA does not show that a fusion is expressed, which is why implementation programmes pair WGS with RNA sequencing.[3]

Clinical applications

Diagnosis and therapeutic stratification

In advanced non-squamous non-small cell lung cancer (NSCLC), guidelines recommend testing for *EGFR*, *ALK* and *ROS1* and for further drivers including *BRAF*, *KRAS*, *MET*, *RET*, *ERBB2* and *NTRK*, preferably within one NGS assay.[16,17] Driver prevalence varies with ancestry: in a global systematic review, *EGFR* mutation frequency in adenocarcinoma ranged from 47% in Asia-Pacific studies to 12% in Oceania,[18] and was 51.4% in the Asian PIONEER cohort.[19] Among 1,230 Indian patients with NSCLC tested by NGS, *EGFR* alterations were found in 33.7% and a guideline-recommended driver in 64.8%, yet only 62.1% of driver-positive patients received targeted therapy.[20]

In cancer of unknown primary (CUP), the randomised CUPISCO trial showed longer progression-free survival with molecularly guided therapy than with continued chemotherapy (median 6.1 vs 4.4 months; hazard ratio (HR) 0.72, 95% confidence interval (CI) 0.56 to 0.92), using panel-based CGP.[21] WGS adds a different capability: genome-wide mutation patterns can predict tissue of origin. A WGS-based classifier

integrated into routine work-up assigned a primary tumour type in 49 of 72 patients with CUP (68%),[22] and an independent classifier in 82 of 141 (58%),[23] although whether such predictions improve outcomes is untested.

The case for WGS is strongest where SVs define disease. In a paediatric cohort, three-platform sequencing (WGS, WES and RNA sequencing) detected 98% of known pathogenic variants, compared with 78% for WES plus RNA sequencing;[24] in the subsequent Genomes for Kids study, WGS enabled detection of activating fusions and enhancer hijacking in 36% and 8% of tumours.[25] In acute myeloid leukaemia (AML) and myelodysplastic syndromes, where genetic risk groups direct consolidation,[26] WGS detected all 40 recurrent translocations and 91 copy number alterations identified by cytogenetics; among 117 patients sequenced prospectively it provided new genetic information in 24.8% and changed the risk category in 16.2%.[27]

Composite biomarkers

The US Food and Drug Administration's tumour-agnostic approval of pembrolizumab for TMB-high tumours (≥10 mutations per megabase) rested on KEYNOTE-158, in which TMB was measured with a commercial CGP panel,[28] and TMB-high status does not predict response in all cancer types.[29] For homologous recombination deficiency (HRD), HRD-positive status on a tumour assay defined the population that benefited from olaparib plus bevacizumab in PAOLA-1.[30] The WGS-based HRDetect classifier identifies *BRCA1/2*-deficient tumours with high sensitivity,[31] and WGS found HRD in 40% of high-grade serous ovarian cancers in the 100,000 Genomes Project,[32] but the value of WGS-defined HRD for predicting benefit from poly(ADP-ribose) polymerase (PARP) inhibitors is less established. In both cases the biomarker that changes prescribing was established in trials that did not use WGS.

Pre-analytics and integrated reporting: the pathologist's role

Platform choice is constrained by decisions made at the grossing bench, before any molecular request is written.

Fixation

Routine pathology relies on formalin-fixed paraffin-embedded (FFPE) tissue, and formalin fixation introduces sequencing artefacts;[14] WGS from FFPE tissue is feasible but inferior to WGS from fresh-frozen tissue.[33] Cold ischaemia time, fixative and fixation duration should be controlled and recorded, yet this is rarely required in routine practice.[34] WGS programmes need fresh or fresh-frozen tissue to be set aside at biopsy or resection, a decision that precedes the diagnosis it is meant to refine. At a specialist sarcoma centre recruiting to the 100,000 Genomes Project, samples from about 400 of nearly 1,000 patients were never sequenced, largely because of necrosis after neoadjuvant treatment or placement in formalin; storing resection specimens at 4°C for up to 96 hours and removing access to formalin improved compliance.[35]

Decalcification

Decalcification degrades nucleic acids. Among 34 decalcified lung cancer bone metastases, amplicon NGS gave invalid results in more than half, and molecular status remained undetermined in five (15%) even after Sanger sequencing.[36] In a comparison of decalcification procedures in breast tumours, all reduced DNA and RNA quantity and quality, and EDTA-based decalcification was preferred because it best preserved nucleic acids.[37] Soft-tissue components should be sampled separately before decalcification whenever molecular testing is anticipated.

Tumour cell fraction

Validated tumour WGS requires at least 20% tumour cells,[14,38] whereas deep panels tolerate less. The estimate on which this triage depends is unreliable: when nine pathologists assessed 47 lung tumour slides, a third of estimates deviated from the manually counted value by at least three categories on an 11-category scale.[39] An overestimate sends an inadequate sample for WGS; an underestimate withholds it (figure 1, step 3). Marking tumour-rich areas for macrodissection, and counting when a sample lies near a threshold, are simple safeguards. Very small, low-cellularity samples were the main cause of panel failure in a large clinical series, and an optimised workflow raised success from 88% to 95%.[40]

Quality assurance and reporting

Each variant class (SNVs, indels, CNVs, SVs and fusions) must be validated with defined limits of detection, and both assay and bioinformatics pipeline maintained under ISO 15189 or equivalent accreditation.[8,41] External quality assessment (EQA) exposes weaknesses that internal validation misses: among 514 deviating EQA results for oncology biomarkers, no corrective action was taken in 27.6%, most often for pre-analytical problems and complex techniques such as NGS.[42] Finally, a genomic result is one component of a diagnosis. WGS does not replace immunohistochemistry for hormone receptors, HER2, PD-L1 or mismatch repair proteins. Results should be issued as an integrated report that reconciles morphology, immunophenotype and genomics and should be discussed at a molecular tumour board; even centralised sequencing requires local expertise to interpret variants in clinical context.[43]

Critical appraisal of WGS in routine services

What routine programmes show

In the Dutch WIDE study, WGS was performed in parallel with standard diagnostics in 1,200 consecutive patients with metastatic cancer.[14] The headline results are favourable: WGS identified 99.2% of biomarkers in regions covered by both approaches, 936 therapy options compared with 343 from standard testing, and 49 previously unrecognised pathogenic germline variants; turnaround was a median of 12 working days. Three qualifications are needed. First, WGS succeeded in only 70% of tumour-containing samples (854 of 1,216), mainly because tumour purity was below 20%; WGS therefore failed in nearly one sample in three, although panel and fusion testing still succeeded in 87% of failed cases that had an indication for molecular testing. Second, the concordance figure applies only to regions both tests cover and does not address low-frequency variants that only deep sequencing detects. Third, options are not treatments: 791 of the 936 options were experimental, and of 603 patients with actionable biomarkers, 147 (24%) had started biomarker-based therapy at a median follow-up of 14 months. Fresh-frozen logistics were readily adopted, but this was a single comprehensive cancer centre working with a dedicated sequencing facility; WGS became a routine test there in January 2021.[44]

In England, routine WGS of 282 tumours from children with suspected cancer reproduced all 738 standard-of-care molecular tests, added disease-relevant findings in 29% and changed management in about 7%.[45] Stated the other way, management was unchanged in about 93% of cases; the demonstrated gain is consolidation of many tests into one more than a change in treatment. In sarcoma, routine WGS at one UK centre refined the diagnosis in 37% of cases and identified a potential therapeutic target in 33%, although six of 73 samples (8%) yielded insufficient DNA.[15] A Dutch series reported a revised diagnosis in 12 of 83 patients (14%),[46] and sarcomas had the highest rate of actionable SVs (13%) in the 100,000 Genomes cohort.[32] These are uncontrolled, largely single-centre cohorts that report diagnostic yield, not patient outcomes. The median turnaround of 5 days reported for myeloid WGS likewise comes from a streamlined workflow in a single-centre study.[27]

Because a tumour genome is complete, a newly validated DNA biomarker requires only a change to the bioinformatic or reporting pipeline,[14] but reanalysis cannot replace re-biopsy when the question is acquired resistance.

Analytical and interpretive limits

Depth is the principal analytical limit. At 20% purity and 100× depth, and assuming a diploid, copy-neutral locus, about 20 reads derive from tumour cells and a clonal heterozygous variant is supported by about 10 (variant allele frequency approximately 10%); subclonal variants have fewer still. Standard sequencing depths are inadequate for impure or clonally heterogeneous tumours,[47] and deep panels with detection limits of 2–5% are more sensitive in this setting.[7]

Validation is achievable but conditional. A Dutch multicentre validation reported 98.5% sensitivity and 97.8% precision for SNVs and indels, with 95.6% technical success in fresh-frozen samples containing at least 20% tumour cells:[38] precisely the requirement that 24% of tumour-containing samples in WIDE did not meet.[14]

Interpretation is the largest recurring burden. A human genome differs from the reference at 4–5 million sites,[48] and a tumour adds thousands of somatic variants to be filtered; the constraint has shifted from generating data to analysing it.[3,49] Tumour–normal sequencing also uncovers germline findings: among

1,040 patients with advanced cancer, 17.5% carried clinically actionable germline variants, more than half of which (101 of 182) guideline-based testing would have missed.[50] Secondary findings in a defined gene list are recommended for reporting with patient opt-out,[51] and demand on genetic counselling and cascade testing rises accordingly.

Turnaround comparisons need care. The medians of 12 working days in WIDE and 5 days in the myeloid study come from dedicated centres.[14,27] In a routine NHS sarcoma service, the median interval from receipt of samples and consent to the genomic tumour advisory board was 35 days (range 20–83).[15] Panel testing varies as widely: tissue NGS took a median of 26 days in a real-life multicentre study,[52] against 12 days for a large plasma panel within a national precision medicine programme.[53] Turnaround depends more on the delivery pathway than on the platform, and best-case WGS should not be set against typical panel figures.

Targeted comparators

For each indication in which WGS is advocated there is a targeted alternative that answers the diagnostic question. In bone and soft tissue tumours, an anchored multiplex PCR RNA fusion panel succeeded in 86% of samples, was 90% concordant with fluorescence in situ hybridisation (FISH) and reverse transcriptase PCR, and detected fusions those methods missed, including novel partners.[54] In central nervous system tumours, array-based DNA methylation profiling changed the diagnosis in up to 12% of prospective cases[55] and has been extended to sarcoma;[56] short-read WGS does not provide this information. In haematology, optical genome mapping identified all clinically relevant SVs and CNVs reported by standard cytogenetics in 100 AML cases when the clone exceeded 5% allele fraction, and additional clinically relevant findings in 13%.[57] None of these methods yields genome-wide small-variant or signature data, but each has a far smaller interpretive burden, and a service considering WGS should first ask whether the targeted comparator is already delivered reliably (table 2, step 2).

Cost and outcome evidence

Micro-costing studies put tumour–normal WGS at £6,841 per cancer case in an NHS laboratory, with consumables accounting for 68–72%,[58] and at €2,925 in the Dutch centralised facility, compared with €58 for three-amplicon Sanger sequencing.[59] An earlier systematic review found that few cost analyses were

transparent and that most studies concerned neurological or neurodevelopmental disorders.[60] In advanced NSCLC, early Dutch modelling found that WGS as the diagnostic test gained 0.002 quality-adjusted life-years (QALYs) at an additional €1,534 per patient and was cost-effective only if priced at about €2,000 while identifying 2.7% more actionable patients.[61] A 2026 update lowered the incremental cost-effectiveness ratio from €737,197 to €419,053 per QALY, still several times the €80,000 threshold used in the original model; diagnostic costs would need to fall from €2,180 to €1,246, or additional druggable targets be found in at least 3.3% of patients.[62]

We found no randomised trial comparing WGS with panel testing. Randomised evidence for profiling-guided therapy comes from panel-based CGP: CUPISCO in CUP,[21] and the ROME trial, in which tailored therapy selected by a molecular tumour board from tissue and plasma CGP improved overall response rate (17.5% vs 10%) and progression-free survival (median 3.5 vs 2.8 months; HR 0.66, 95% CI 0.53 to 0.82) over standard care, without an overall survival difference at 52% crossover.[63] Only 400 of 1,794 screened patients were randomised. These trials support comprehensive profiling with expert review where matched drugs are available; they do not show that sequencing the whole genome adds benefit.

Resource-limited health systems: the case of India

The constraints described so far are those of well-funded systems. In low- and middle-income countries they are amplified at every step, and they should determine test choice. We use India as the example.

Tissue and laboratory capacity

Diagnostic pathology is built on FFPE tissue,[14] so WGS would require new fresh-tissue pathways from the operating theatre and biopsy suite to a genome laboratory. Tissue already limits panel testing. In a pathology-led staggered reflex testing programme for NSCLC at an Indian tertiary centre, tissue inadequacy or test failure prevented complete biomarker evaluation in 40.1% of 867 cases, and 35.1% of samples referred for a 40-gene panel failed pre-library quality requirements.[64] A test with stricter purity and DNA requirements can be expected to fail more often. Laboratory accreditation in India is assessed by the National Accreditation Board for Testing and Calibration Laboratories; staff at an accredited government

laboratory described heavy documentation and financial burdens,[65] and validating WGS for every variant class would add substantially to them.[8,41]

Cost and reimbursement

CGP in India is not widely available because of cost and limited expertise: tests have been reported to cost US$200–1,500, take 3–4 weeks and are often performed at a centre away from where the patient is treated.[66] Tumour–normal WGS, micro-costed at €2,925 to £6,841 in European laboratories,[58,59] lies above this range before any local infrastructure is built. Who pays matters as much as the price. In a survey of 14 oncologists from 11 Asia-Pacific countries, India was among the countries reporting no government funding for sequencing tests, with private insurance cover limited by policy conditions or financial caps, and every respondent cited prohibitive test cost as a barrier.[67] Diagnostics already account for 36% of out-of-pocket spending on outpatient cancer care in India, where 80% of patients treated as outpatients incur catastrophic health expenditure.[68] Insurance ceilings leave most patients who start targeted therapy paying out of pocket.[66]

Access to matched therapy

A test benefits patients only if the indicated treatment can be obtained. In the Indian NSCLC series, more than a third of patients with a targetable driver did not receive targeted therapy, and in an unadjusted comparison median overall survival among driver-positive patients was 26.7 months with targeted therapy and 9.3 months without.[20] In a multicentre Indian cohort of 221 patients with advanced cancer who had CGP, 21 (10%) received targeted therapy on the basis of the result and nine (4%) had clinical benefit.[69] ESMO makes its tumour-agnostic sequencing recommendation conditional on access to matched therapies.[6] Where access is the binding constraint, a test that lengthens the list of unaffordable options adds cost without utility; this is why the algorithm begins with a utility gate (figure 1, step 1).

Population reference data

Germline filtering and variant classification depend on population reference data, in which India has been under-represented.[70] In WGS of 1,029 healthy Indian individuals, about 55% of SVs were absent from public global datasets.[71] The GenomeIndia project has now reported a variant call-set from 9,772 individuals

in 83 populations, in which 65% of variants are ultra-rare.[72] Such resources must be incorporated into clinical pipelines, and their effect on misclassification measured, before WGS is reported locally.

Data protection and counselling

The Digital Personal Data Protection Act 2023 requires consent for the processing of personal data to be free, specific, informed, unconditional and unambiguous, and gives individuals the right to withdraw it (section 6).[73] A genome identifies an individual and is informative about relatives, so a laboratory that generates and stores genomes takes on a larger consent and data-governance task than a panel service handling far less data. Counselling capacity is a further limit: cancer genetics clinics in India remain unevenly implemented because of infrastructural and socioeconomic barriers,[74] and tumour–normal WGS, which revealed pathogenic germline variants in 70 of 848 patients (8%) in WIDE,[14] would add demand that these services cannot yet meet.

Implications

For most such settings the priorities are sequential: secure pre-analytics; deliver guideline-mandated single-gene or small-panel testing reliably; add validated CGP where matched drugs are accessible; and refer paediatric, acute leukaemia and sarcoma cases, for which fresh tissue or marrow can be shipped, to a small number of accredited national hubs for WGS (table 2, step 4). Pathology-led staggered workflows of this kind are already operating.[64]

Existing frameworks and what a capability-tiered model adds

NHS England commissions WGS for children with cancer[43] and for sarcoma,[15] with acute leukaemia among the other indications listed in its National Genomic Test Directory, alongside panel testing for common adult tumours.[4] ESMO recommends tumour NGS in advanced non-squamous NSCLC, prostate, colorectal and ovarian cancer and cholangiocarcinoma, extended in 2024 to breast cancer and rare tumours including sarcoma and CUP; its recommendations are framed by actionability, cost-effectiveness and accessibility and do not mandate a platform.[5,6] Our list of indications (table 2) is deliberately consistent with both. The indications are not what is new.

Both frameworks assume the capabilities of the systems that wrote them. The model proposed here adds four elements, which form the first four steps of the algorithm (figure 1) and the corresponding sections of table 2. First, access to matched therapy is an explicit gate (step 1). Second, each WGS indication is paired with the targeted comparator to use when WGS is unavailable or unsuitable (step 2). Third, the choice is conditional on the specimen: fresh tissue and its tumour cell fraction determine whether WGS can succeed at all (step 3). Fourth, it defines three tiers of capability (step 4): tier 1, local laboratories working from FFPE with single-gene and small-panel tests; tier 2, regional laboratories with validated CGP, RNA fusion panels, cytogenetics and a molecular tumour board; and tier 3, national hubs with accredited WGS and a fresh-tissue referral pathway. Every route ends in an integrated report and tumour board review (step 5), and each recommendation in table 2 carries a statement of evidence strength and the tier that delivers it. The model is a proposal and has not been validated; prospective audit of failure rates, turnaround and treatment uptake at each tier is the necessary next step.

Future directions

Three developments could shift this balance. Long-read sequencing resolves repetitive regions and complex SVs and reads DNA methylation directly from native DNA, potentially combining genome and methylome in one assay.[75] Deep-learning callers such as DeepSomatic now support tumour-only and FFPE samples on short-read and long-read platforms,[76] which may weaken the fresh-frozen requirement. Plasma WGS can integrate genome-wide mutation signals for sensitive disease monitoring.[77] Each will need the same scrutiny of failure rates, cost and outcomes applied here.

Conclusion

Panels, exomes and genomes occupy complementary niches. WGS gives the broadest view of tumour DNA, and routine programmes show it can be delivered; they also show that it fails in a substantial minority of samples, that most additional findings do not change treatment, and that neither outcome nor cost-effectiveness evidence yet favours it over panel testing. Existing frameworks already limit WGS to indications defined by structural complexity or diagnostic uncertainty. We add that the choice should be conditional on access to treatment, the specimen and the capability of the laboratory and health system, and

that every WGS indication has a targeted comparator. Where pathology is FFPE-based, testing is paid for out of pocket and drug access is incomplete, reliable pre-analytics and validated panels, with hub referral of selected cases for WGS, will deliver more benefit than universal genome sequencing.

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Table 1 Comparison of targeted gene panels, whole exome sequencing and whole genome sequencing in cancer diagnostics

Feature	Targeted panels (hotspot to CGP)	Whole exome sequencing	Whole genome sequencing
Genomic target	Selected hotspots to several hundred genes[7]	Exons of about 20,000 genes (1–2% of genome)[10]	Whole genome, coding and non-coding[12]
Typical tumour depth	Deep; detection limit about 2–5% VAF[7]	75–100×[47]	About 90–100× (germline 30–40×)[14,15]
Variant classes	SNVs and indels in targets; with hybrid-capture panels also CNVs, structural rearrangements and TMB[7,9]	SNVs and indels exome-wide; limited CNVs; poor SV detection; TMB	SNVs, indels, CNVs, SVs, non-coding variants, mutational signatures, TMB, MSI, HRD;[14,38] expressed fusions need RNA confirmation[3]
Low-purity samples	Most sensitive	Intermediate	Least sensitive; at least 20% tumour cells required[38]
Sample requirements	FFPE; low DNA input; plasma	FFPE feasible; matched normal preferred	Fresh or fresh-frozen tissue and matched normal; FFPE inferior[33]
Reported failure in routine use	Variable; 35% of referred samples failed pre-library quality control in one resource-limited setting[64]	Not established	30% of tumour-containing samples (WIDE);[14] 8% insufficient DNA in a sarcoma service[15]

Feature	Targeted panels (hotspot to CGP)	Whole exome sequencing	Whole genome sequencing
Turnaround	Medians of 26 days (tissue) and 12 days (plasma) reported in routine practice;[52,53] 3–4 weeks for CGP in India[66]	Variable; mainly research use	Median 5 days to 12 working days in dedicated centres;[14,27] median 35 days in a routine NHS sarcoma service[15]
Micro-costed price	From €58 for single-gene Sanger sequencing upwards[59]	Not established	€2,925 to £6,841 per tumour–normal case[58,59]
Bioinformatic and interpretive burden	Lowest	Intermediate	Highest
Main clinical role	Most adult solid tumours; low-purity, scant or degraded samples	TMB calibration; research	Paediatric cancers, acute leukaemia, sarcoma and selected diagnostically complex cases, where specimen and capability allow

CGP, comprehensive genomic profiling; CNV, copy number variant; FFPE, formalin-fixed paraffin-embedded; HRD, homologous recombination deficiency; indel, small insertion or deletion; MSI, microsatellite instability; SNV, single nucleotide variant; SV, structural variant; TMB, tumour mutational burden; VAF, variant allele frequency. Values are typical ranges from the cited sources and vary by laboratory and assay.

Table 2 A proposed indication-led, capability-tiered model for choosing between WGS and targeted testing. Rows follow the steps of figure 1

Setting	Suggested test	Rationale	Evidence strength*	Delivered at†
Step 1. Utility gate				
Result would not change management, or matched therapy not accessible	Limited testing: guideline-mandated single-gene tests and immunohistochemistry only	More than a third of driver-positive patients untreated, and 10% treated after CGP, in Indian series[6,20,69]	Low to moderate: observational; guideline consensus	Tier 1
Step 2. Indication (WGS only if steps 3 and 4 are also met; otherwise the targeted comparator)				
Paediatric cancers	WGS with RNA sequencing. Comparator: RNA fusion panel with DNA panel	High burden of SVs, fusions and germline predisposition; routine WGS reproduced all standard tests and changed management in about 7%[25,45]	Moderate: prospective implementation cohorts; no comparative outcome data	Tier 3; comparator tier 2

Setting	Suggested test	Rationale	Evidence strength*	Delivered at†
Acute leukaemia and MDS	WGS. Comparator: karyotype and FISH or optical genome mapping, with a myeloid panel	WGS reproduced cytogenetics and changed risk category in 16.2%; optical genome mapping matched standard cytogenetics[27,57]	Moderate: single-centre prospective and multicentre retrospective comparisons	Tier 3; comparator tier 2
Sarcoma	WGS. Comparator: RNA fusion panel with DNA panel	Diagnosis refined in 14–37% in routine WGS series; RNA fusion panels are 90% concordant with FISH and RT-PCR[15,46,54]	Moderate: uncontrolled single-centre cohorts	Tier 3; comparator tier 2
Unfavourable CUP	CGP panel first. If unresolved: WGS with a tissue-of-origin classifier; otherwise act on the CGP result	Randomised benefit with panel-guided therapy;[21] WGS classifiers assigned a primary in 58–68%[22,23]	High for CGP-guided therapy; low for WGS classifiers (no outcome data)	Tier 2; WGS tier 3

Setting	Suggested test	Rationale	Evidence strength*	Delivered at†
Central nervous system tumours	Methylation array with DNA panel; WGS does not replace methylation profiling	Methylation profiling changed diagnosis in up to 12%[55]	Moderate: prospective diagnostic cohort	Tier 2
Common adult solid tumours (eg, NSCLC)	Guideline-directed panel on tissue or plasma	Covers guideline-recommended targets; randomised evidence is panel-based[6,17,63]	High for panels; none that WGS improves outcomes	Tiers 1–2
Step 3. Specimen (overrides step 2)				
Tumour cell fraction below 20% or scant tissue	Macrodissection; deep panel or single-gene test; plasma ctDNA	Depth needed to detect low-VAF variants; low purity was the main cause of WGS failure[14,40,47]	Moderate: consistent observational data	Tiers 1–2
FFPE-only or decalcified tissue	Panel testing; EDTA-based decalcification and separate undecalcified sampling	FFPE WGS is inferior; decalcification degrades nucleic acids, least with EDTA[33,36,37]	Moderate: observational	Tiers 1–2
Step 4. Capability				

Setting	Suggested test	Rationale	Evidence strength*	Delivered at†
No fresh-tissue pathway or accredited WGS laboratory in house	Refer step 2 WGS indications to a national hub; if referral is not possible, use the targeted comparator	Validation and accreditation burden; staggered pathology-led workflows are feasible[41,64]	Low: single-centre audit and expert opinion	Tier 2, referring to tier 3
Step 5. Reporting				
All tested patients	Integrated report reconciling morphology, immunophenotype and genomics; molecular tumour board; germline findings to genetic counselling	Centralised sequencing still needs local interpretation; tumour–normal sequencing revealed pathogenic or actionable germline variants in 8–17.5%[14,43,50]	Low: implementation experience and expert opinion	All tiers; tumour board at tier 2 or 3

*High: randomised trials or guideline recommendations based on them. Moderate: prospective implementation or diagnostic cohorts with consistent findings. Low: retrospective series, modelling or expert opinion. †Tier 1, local laboratory (FFPE; single-gene tests and small panels); tier 2, regional laboratory (validated CGP, RNA fusion panels, cytogenetics, molecular tumour board); tier 3, national hub (accredited WGS with a fresh-tissue referral pathway). CGP, comprehensive genomic profiling; ctDNA, circulating tumour DNA; CUP, cancer of unknown primary; FFPE, formalin-fixed paraffin-embedded;

FISH, fluorescence in situ hybridisation; MDS, myelodysplastic syndromes; NSCLC, non-small cell lung cancer; RT-PCR, reverse transcriptase PCR; SV, structural variant; VAF, variant allele frequency; WGS, whole genome sequencing.

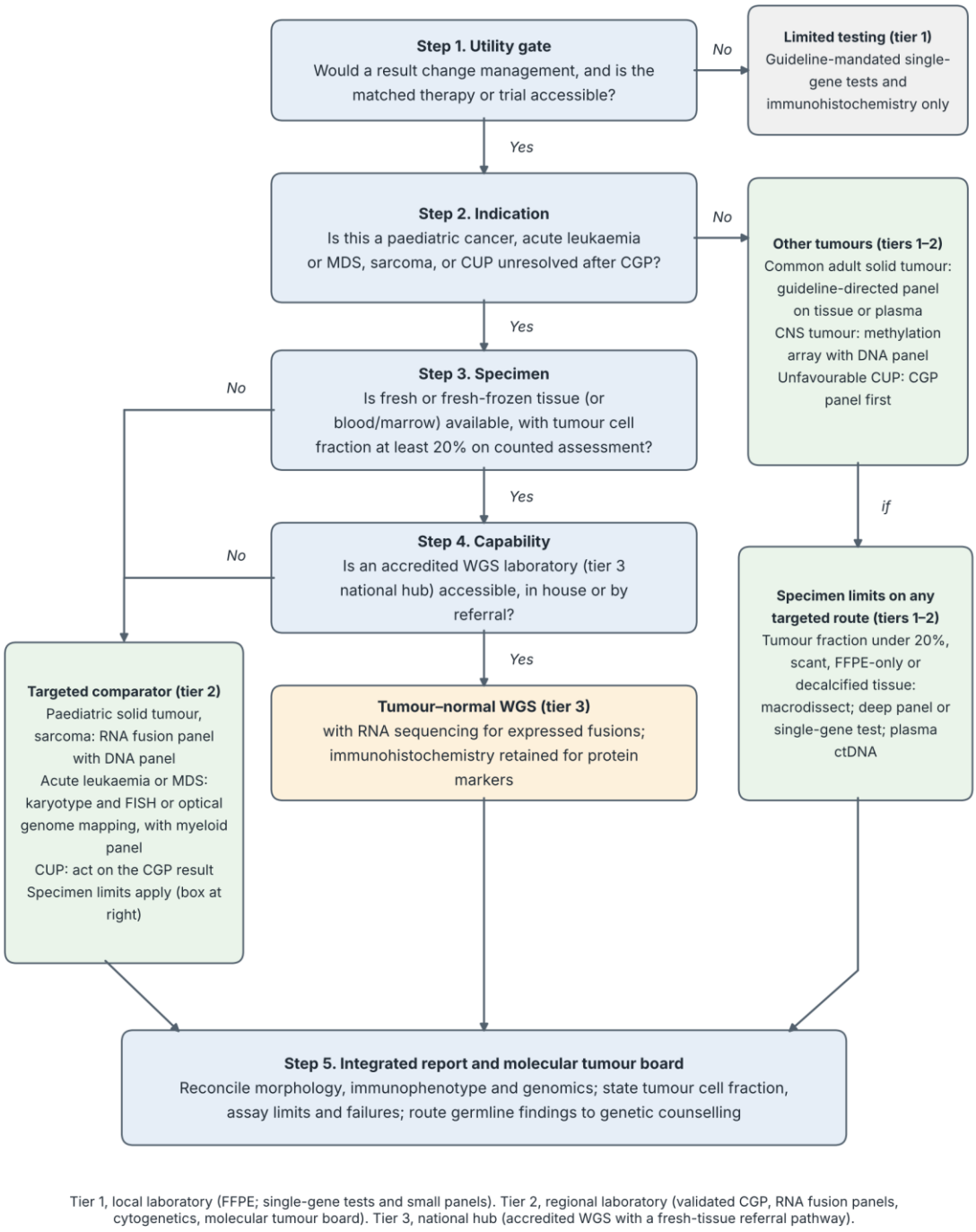


Figure 1 Five-step decision algorithm for platform choice. The steps correspond to the sections of table 2. WGS is selected only when a step 2 indication, a fresh specimen with adequate tumour cell fraction (step 3) and access to an accredited laboratory (step 4) are all present; otherwise the targeted comparator for that indication is used. Specimen limits apply to every targeted route. Tier 1, local laboratory; tier 2, regional laboratory; tier 3, national hub. CGP, comprehensive genomic profiling; CNS, central nervous system; ctDNA, circulating tumour DNA; CUP, cancer of unknown primary; FFPE, formalin-fixed paraffin-

embedded; FISH, fluorescence in situ hybridisation; MDS, myelodysplastic syndromes; WGS, whole genome sequencing.