MDForLives

THE GLOBAL PULSE OF HEALTHCARE · ONCOLOGY & HEMATOLOGY INSIGHT REPORT

Targeted Therapy Resistance: What Changes After Cancer Progression?

Responses from oncologists on primary and acquired resistance to targeted therapy: how often progression triggers repeat molecular testing, what makes a resistance finding actionable, how treatment sequencing changes, and why the main post-progression barrier may sit beyond the test itself.

Progression → Resistance signal → Molecular interpretation → Next treatment

90	6	72.2%	8975843
Survey records	Countries represented USA · UK · Canada · Italy · France · Germany	Completion rate	Survey ID

WHY THIS REPORT

Progression after targeted therapy creates a second precision-oncology problem: identifying what changed and whether that change can be treated.

Targeted therapy is built around a specific biologic dependency. Once disease progresses, the oncologist has to determine whether the original target has changed, whether a bypass pathway has emerged, whether resistant subclones now dominate, or whether progression reflects a broader shift in disease biology. The answer may require tissue, blood, imaging, prior molecular history, and the patient's clinical trajectory to be interpreted together.

The pressure is practical as well as biologic. Repeat molecular testing can identify a resistance mechanism, but that result is only useful if it is valid, timely, clinically relevant, and linked to a treatment that is evidence-supported and available. When those conditions are not met, greater molecular detail can coexist with limited therapeutic leverage.

The MDForLives survey examines how oncologists navigate this transition: how often resistance is encountered, when monitoring begins, how repeat testing is used, what guides the next strategy, what blocks actionability, and which advances clinicians believe could improve resistance management over the next 3–5 years.

Survey lens. MDForLives survey SGID 8975843 includes 90 survey records with a 72.2% completion rate across 6 countries: USA · UK · Canada · Italy · France · Germany. Clinical question bases vary from 68 to 71. Multi-select questions are interpreted at option level. Internal operational, required-text, after-question, and honeypot fields are excluded from analysis.

CLINICAL CONTEXT

Resistance biology can change over time, but repeat testing is most useful when the result can alter a real treatment decision.

The National Cancer Institute notes that targeted therapy resistance can occur when the target itself changes or when cancer cells develop alternative ways to grow that no longer depend on the original target. NCI also explains that tumor biomarkers can change over time, which is one reason a prior molecular profile may no longer fully represent the cancer after recurrence or progression.

ASCO's guidance on somatic genomic testing in metastatic or advanced cancer supports genomic sequencing when a molecular result can guide the use or exclusion of a treatment. Disease-specific guidance can go further: the 2025 ASCO living guideline for advanced NSCLC with driver alterations states that, because new targetable resistance mechanisms can emerge, efforts should be made to assess for new mutations with tissue and/or blood NGS after progression. That is a disease-specific recommendation, not a universal rule for every tumor.

As molecular data become more complex, interpretation also becomes a systems issue. ESMO's 2025 recommendations on molecular tumour boards highlight the value of multidisciplinary expertise and standardized processes for translating complex profiling results into clinical decisions. This is the context in which the MDForLives findings should be read: not as a single cross-cancer testing algorithm, but as a picture of where oncologists see the greatest practical friction after targeted therapy stops working.

Context for interpretation: External guidance defines disease-specific standards and testing boundaries. The MDForLives findings describe respondent-reported practice across six countries and should be interpreted according to the individual cancer type, therapy, assay, regulatory environment, and available treatment options.

EXECUTIVE SUMMARY

Six findings that show why identifying resistance is only one part of the post-progression decision.

01
45.1% encounter targeted therapy resistance frequently
Resistance is common enough to require a planned approach to progression rather than an ad hoc response.

02
63.8% put molecular findings at the center of the next strategy
The resistance mechanism leads, but evidence for available therapy and disease trajectory remain co-drivers.

03
42.0% repeat testing selectively by cancer type and history
Retesting is common but conditional, reflecting differences in disease biology, prior treatment, and likely actionability.

04
44.9% use repeat testing to find actionability or guide sequencing
The two leading purposes are tied, linking molecular explanation directly to the next treatment decision.

05
68.1% say limited effective options are a major barrier
The strongest constraint appears after testing, when a biologically relevant result still may not create a viable therapy.

06
45.6% expect better resistance-targeted therapies to drive the next advance
Respondents put therapeutic actionability ahead of earlier detection alone as the biggest future opportunity.

01
RESISTANCE BURDEN

Targeted therapy resistance is frequent enough to be part of routine oncology planning

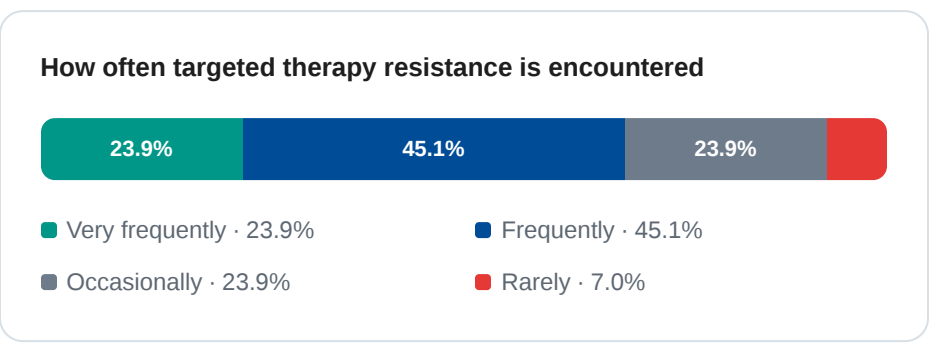
45.1% encounter primary or acquired resistance frequently, and 23.9% very frequently.

CONTEXT
A patient who responds to a targeted therapy may remain clinically stable for months or years before progression forces a new decision. That transition is familiar across multiple molecularly defined cancers, even though the mechanisms and recommended work-up differ by disease and drug class.

WHAT THE DATA SHOWS
Frequently is the largest single response at 45.1%. Another 23.9% select very frequently, 23.9% occasionally, and only 7.0% rarely. The survey therefore places resistance squarely inside everyday oncology practice rather than at the margins.

THE INSIGHT
When resistance is expected, practices can prepare the next-step pathway earlier: preserve access to prior molecular results, identify tissue or blood testing routes, define who reviews complex findings, and know where clinical trials or disease-specific options are available.

WHY IT MATTERS
The clinical cost of waiting until progression is not only time. It can compress biopsy, molecular turnaround, multidisciplinary interpretation, and treatment selection into the same period in which the patient's disease is changing.



02
NEXT-TREATMENT DECISION

Molecular findings lead the next treatment decision, but the plan is still a clinical synthesis

63.8% say molecular findings or the resistance mechanism influence the next strategy after progression.

CONTEXT
After progression, the oncologist is rarely choosing between molecular information and clinical judgment. The problem is how to combine the two quickly enough to select a next line that is biologically plausible, evidence-supported, and appropriate for the patient.

WHAT THE DATA SHOWS
Molecular findings or the resistance mechanism lead at 63.8%, followed by evidence for available treatment options at 58.0% and clinical status or disease trajectory at 53.6%. Prior response, toxicity, and patient factors are selected by 7.2% in this up-to-two response item.

THE INSIGHT
The hierarchy suggests that the molecular result frames the decision, while the evidence base and disease trajectory determine whether that result can be acted on. A resistance alteration can be real without being clinically useful if the matched strategy lacks evidence, access, or fit with the current clinical situation.

WHY IT MATTERS
Post-progression precision medicine is not a one-to-one map from alteration to drug. The next strategy depends on whether the finding explains resistance, whether a matched option is credible, and whether the timing and toxicity profile make sense for the patient.

03
EMERGING RESISTANCE MONITORING

Monitoring before clear progression is used, but not through one universal model

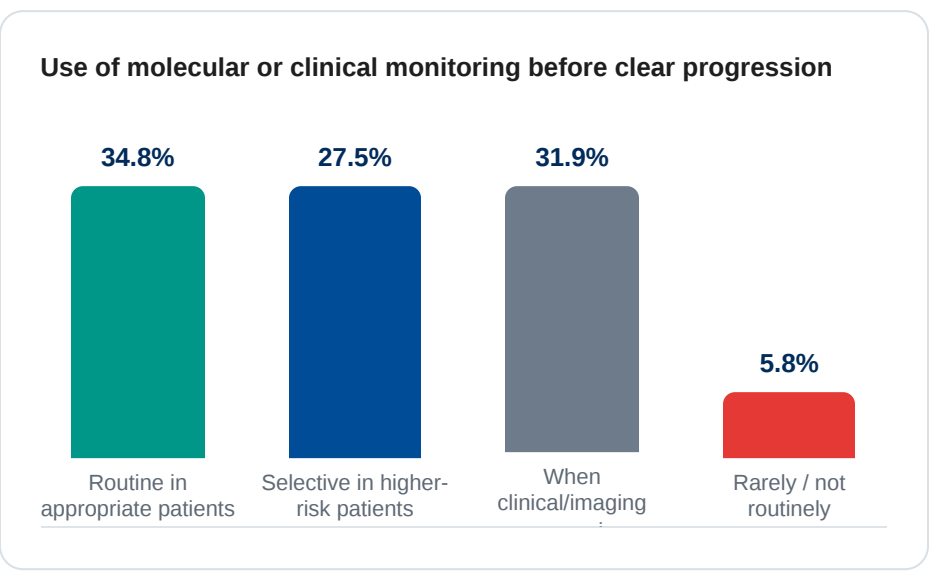
34.8% routinely monitor appropriate patients, while 31.9% mainly escalate monitoring when clinical or imaging concern appears.

CONTEXT
The promise of molecular monitoring is to identify biologic change before progression becomes clinically obvious. The limitation is that the value of earlier detection varies by tumor type, assay, treatment, resistance mechanism, and whether an earlier signal has a validated consequence.

WHAT THE DATA SHOWS
Routine monitoring in appropriate patients is selected by 34.8%. Another 27.5% use it selectively in higher-risk patients, 31.9% mainly when clinical or imaging findings raise concern, and 5.8% rarely or not routinely.

THE INSIGHT
The distribution reflects selective adoption rather than a single standard. Respondents appear to move between proactive and triggered monitoring depending on the likelihood that a molecular signal will be interpretable and actionable.

WHY IT MATTERS
Earlier detection creates value only if it improves the timing or quality of a decision. Otherwise it can create information before the evidence, treatment pathway, or clinical threshold for action is ready.



04
REPEAT MOLECULAR TESTING

Repeat testing is selective, and its two leading goals are tied: find the mechanism and choose the next therapy

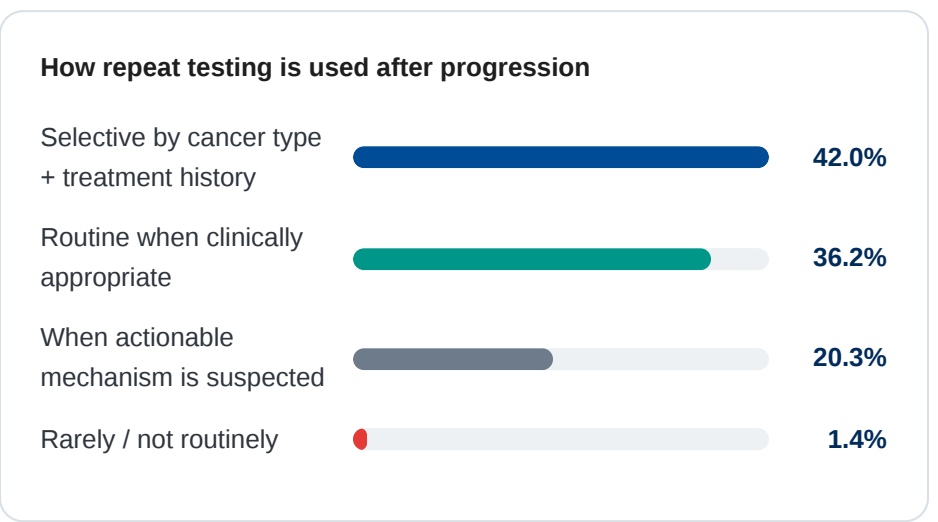
42.0% repeat molecular or biomarker testing selectively by cancer type and treatment history; 44.9% use it to identify an actionable resistance finding and the same 44.9% to guide subsequent therapy sequencing.

CONTEXT
Repeat testing after progression can use tissue, blood, or other disease-specific methods. The practical question is not whether retesting is conceptually useful, but whether the current clinical setting has a plausible resistance mechanism and a decision that new molecular information can influence.

WHAT THE DATA SHOWS
Selective retesting by cancer type and treatment history is the largest approach at 42.0%, followed by routine testing when clinically appropriate at 36.2%. When testing is performed, identifying an actionable mutation or biomarker and guiding selection or sequencing of subsequent therapy are tied at 44.9% each.

THE INSIGHT
The tie links biologic explanation to therapeutic consequence. Respondents are not repeating testing only to document evolution; they are looking for a finding that can justify a different treatment sequence.

WHY IT MATTERS
NCI notes that biomarker profiles can change over time, while disease-specific ASCO guidance in driver-altered NSCLC recommends renewed molecular assessment after progression because new targetable mechanisms can emerge. The survey suggests oncologists apply that logic selectively rather than uniformly across all cancers.



05
TREATMENT SEQUENCING AFTER RESISTANCE

Resistance-guided targeted therapy leads, but one-third still move to another established mechanism

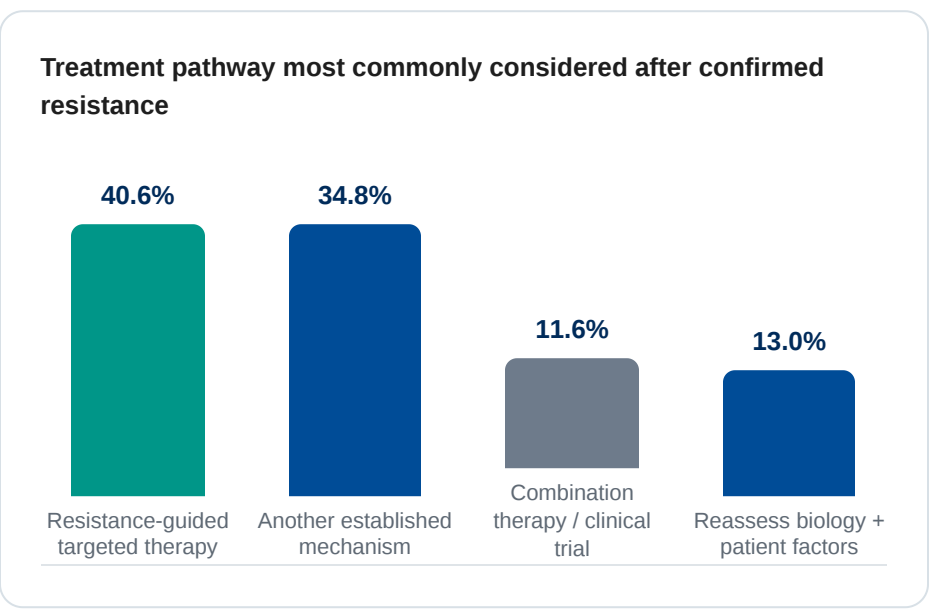
40.6% most commonly consider resistance-guided targeted therapy based on new molecular findings; 34.8% switch to another established treatment mechanism.

CONTEXT
A confirmed resistance mechanism does not automatically dictate a matched targeted strategy. The relevant therapy may not exist, may lack sufficient evidence in the current disease context, may be inaccessible, or may not fit the patient's prior treatment and clinical status.

WHAT THE DATA SHOWS
Resistance-guided targeted therapy is the largest pathway at 40.6%, followed closely by switching to another established treatment mechanism at 34.8%. Combination therapy or a clinical trial is selected by 11.6%, while 13.0% first reassess disease biology and patient factors before choosing the next strategy.

THE INSIGHT
The split shows that molecularly guided sequencing is important but not dominant enough to displace established alternatives. Resistance biology changes the decision set, but it does not eliminate the need for a broader oncology treatment hierarchy.

WHY IT MATTERS
A precision result earns clinical weight only when it improves the risk-benefit balance relative to available standard approaches or a suitable trial. That is why the same progression event can lead to another targeted therapy in one patient and a different treatment mechanism in another.



06
CLINICAL UTILITY OF MOLECULAR INFORMATION

Molecular information usually matters, but not for every patient or every progression event

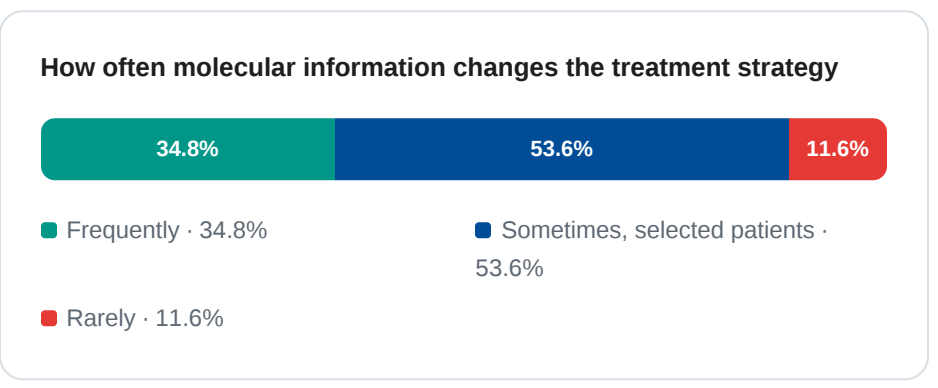
53.6% say molecular information after progression changes treatment sometimes, in selected patients; 34.8% say it changes treatment frequently.

CONTEXT
Clinical utility is the point where molecular information becomes a different treatment decision. That conversion depends on assay validity, the biology identified, available therapies, disease context, access, and whether the patient can receive the option.

WHAT THE DATA SHOWS
Sometimes, in selected patients is the largest response at 53.6%. A further 34.8% say molecular information frequently changes treatment, while 11.6% say it rarely does.

THE INSIGHT
The pattern is neither skeptical nor uniformly enthusiastic. Molecular information is influential, but its treatment impact is conditional. This fits the NCI view that biomarker testing can identify changes that do not help treatment selection when no matched therapy exists or when the finding is not clinically meaningful.

WHY IT MATTERS
The quality metric for repeat testing should not be the number of tests ordered. It is whether the right patient receives a result in time to support a decision that improves the treatment pathway.



07
BARRIERS AFTER PROGRESSION

The largest resistance-management barrier sits after molecular testing: too few effective treatment options

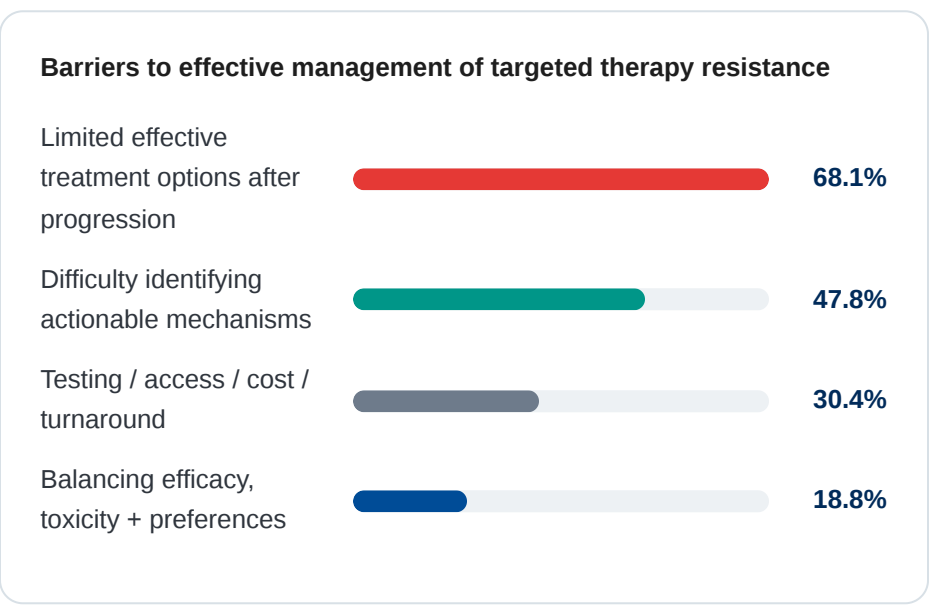
68.1% identify limited effective treatment options after progression as a major barrier.

CONTEXT
Precision oncology is often discussed as a testing problem, but the survey places the strongest friction one step later. Even when resistance is recognized, the next line can remain constrained by the available therapeutic landscape.

WHAT THE DATA SHOWS
Limited effective treatment options after progression lead at 68.1%. Difficulty identifying actionable resistance mechanisms follows at 47.8%, testing, access, cost, or turnaround-time limitations at 30.4%, and balancing efficacy, toxicity, and patient preferences at 18.8%.

THE INSIGHT
The ranking separates information from actionability. Better diagnostics can reduce uncertainty, but they cannot create a therapy where none exists or where a matched option is not accessible, sufficiently supported, or tolerable.

WHY IT MATTERS
The return on molecular testing depends on the therapeutic ecosystem around it: targeted drugs, combination strategies, trials, reimbursement, timely access, and expert interpretation. Improving only one layer will leave the rest of the resistance pathway constrained.



08
NEXT 3–5 YEARS

Oncologists expect better resistance-targeted therapies to matter more than earlier detection alone

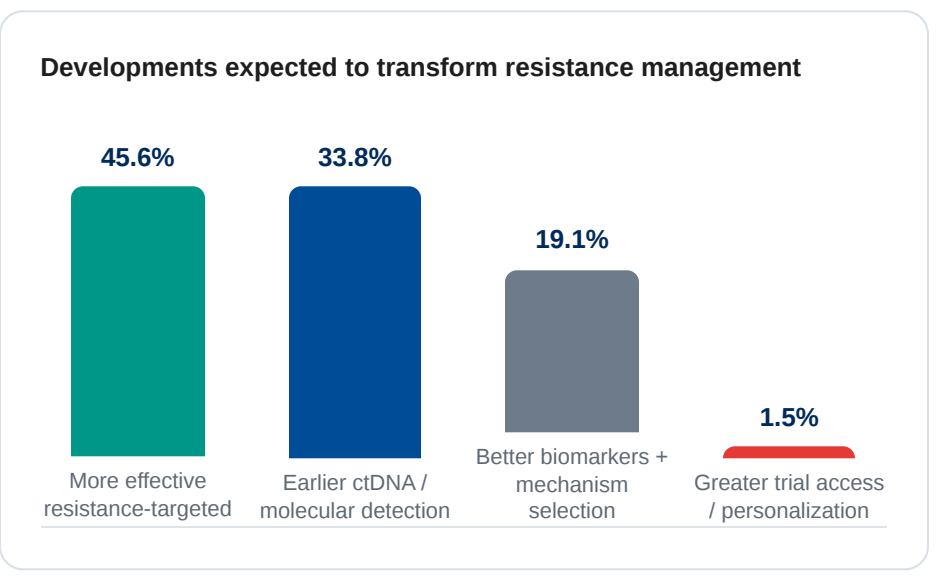
45.6% choose more effective resistance-targeted therapies and combinations as the development most likely to transform management.

CONTEXT
ctDNA, repeat NGS, and molecular monitoring are increasingly visible in precision-oncology research and selected clinical pathways. But earlier knowledge only changes outcomes when there is a validated action to take on that knowledge.

WHAT THE DATA SHOWS
More effective resistance-targeted therapies and combinations lead at 45.6%. Earlier resistance detection through ctDNA and molecular monitoring follows at 33.8%, better biomarkers and mechanism-based selection at 19.1%, and greater trial access or personalized treatment strategies at 1.5%.

THE INSIGHT
Respondents prioritize therapeutic consequence over detection technology. The ranking is consistent with the barrier data: the central unmet need is not simply to see resistance sooner, but to have a more effective next move once it is seen.

WHY IT MATTERS
The future resistance pathway will be strongest when earlier molecular detection, standardized interpretation, and a broader portfolio of resistance-specific therapies advance together rather than as separate innovations.



OPEN-ENDED ANALYSIS

When oncologists describe the case they wish had gone differently, they return to mechanism clarity, earlier molecular information, and a treatment that can actually use the result.

Respondents were asked to think about a patient whose cancer progressed despite an initial response to targeted therapy and describe the key challenge in understanding or managing resistance, plus one change in molecular testing, treatment sequencing, or emerging therapy that could have improved the outcome.

Actionable mechanism clarity
Several responses describe difficulty identifying the resistance clone, separating tumor heterogeneity from a true driver, or understanding which pathway had become dominant after progression.

Earlier and more repeatable testing
Clinicians mention more frequent molecular monitoring, repeat biopsy, liquid-biopsy or NGS access, and standardized testing as ways to recognize resistance sooner or with greater confidence.

Better next-line efficacy
A recurring concern is that testing may identify resistance while the available second-line or resistance-directed treatment remains weak, uncertain, or absent.

Stronger test-to-treatment linkage
Some responses focus on better correlation between molecular results and treatment selection, including clearer evidence about which finding should change sequencing.

Multidisciplinary interpretation
Close follow-up and multidisciplinary review appear in the qualitative responses as ways to combine molecular data, imaging, clinical trajectory, and therapeutic options more coherently.

Minority and divergent views
Not every response centers on more testing. Some emphasize treatment efficacy itself, biopsy logistics, or broader support. One response did not provide a clinically interpretable answer and was not forced into a theme.

Qualitative interpretation note. Responses were submitted in multiple languages and are summarized at the meaning level. Themes are descriptive and are not assigned weighted percentages because the open-ended material was not formally coded as a quantitative dataset.

FREQUENTLY ASKED QUESTIONS

Frequently asked questions about targeted therapy resistance.

What is targeted therapy resistance in cancer?
Targeted therapy resistance occurs when a cancer does not respond to a targeted treatment from the outset or stops responding after an initial benefit. Resistance can reflect changes in the original target, activation of alternative growth pathways, tumor heterogeneity, or other biologic adaptations.

What is the difference between primary and acquired resistance?
Primary resistance means the cancer shows little or no meaningful response to a targeted therapy from the beginning. Acquired resistance develops after an initial response or period of disease control, when the tumor evolves in a way that reduces treatment effectiveness.

When should molecular testing be repeated after cancer progression?
Repeat molecular testing is most useful when a new result could change management. The timing and test type depend on the cancer, previous therapy, suspected resistance mechanisms, available targeted options, tissue access, and current disease-specific guidance.

How can ctDNA help in targeted therapy resistance?
Circulating tumor DNA can identify some tumor-derived molecular changes through a blood sample and may help detect emerging or acquired resistance in selected settings. Its clinical role varies by cancer type and assay, and a negative blood result does not always exclude a relevant tumor alteration.

Does finding a resistance mutation always change treatment?
No. A resistance finding is clinically useful only when it is sufficiently validated, relevant to the current cancer and treatment history, and linked to an available or appropriate treatment strategy, clinical trial, or other actionable decision.

What happens when no actionable resistance mechanism is found?
Management may rely on the broader clinical picture, including disease trajectory, prior response, toxicity, patient goals, established treatment options, and clinical-trial availability. In selected cases, further tissue or blood testing may be considered when it could clarify the next decision.

ONCOLOGY DECISION LENS

What this means at four decision points after targeted therapy begins to fail.

The survey does not define one cross-cancer algorithm. It does show where oncologists repeatedly need the pathway to be clearer: when to look, what to test, how to interpret the result, and what to do when the finding is not actionable.

At the first resistance signal
Define the question before ordering the test. Is the goal to explain progression, identify a new target, confirm persistence of the original target, or determine whether the patient should move to a different treatment mechanism?

When choosing tissue, blood, or both
Match the sample strategy to the disease and decision. Assay sensitivity, tissue availability, tumor biology, prior treatment, and disease-specific guidance determine whether liquid biopsy, tissue biopsy, or complementary testing is appropriate.

When a new alteration appears
Separate biologic plausibility from clinical actionability. Ask whether the finding is a validated resistance mechanism, whether a matched therapy has meaningful evidence, and whether the option is accessible and appropriate now.

When no matched therapy exists
Return to the full oncology decision. Disease trajectory, established alternatives, toxicity, patient goals, trial availability, and multidisciplinary review may matter more than molecular specificity when the result does not create an effective next line.

CLOSING PERSPECTIVE

The next precision-oncology gain is not simply detecting resistance sooner. It is making the resistance signal more actionable.

The survey describes an oncology pathway in which molecular information is already central, but not sovereign. Resistance is encountered frequently. Molecular findings influence the next strategy. Repeat testing is common in selected settings. And when resistance is confirmed, a new molecularly guided targeted therapy is the most selected next pathway.

Yet the strongest barrier is limited effective treatment options after progression. That finding changes the interpretation of everything upstream. Earlier ctDNA detection, repeat NGS, better biomarkers, and more sophisticated molecular interpretation are valuable, but their impact is bounded by the therapies, evidence, trial access, and treatment infrastructure available after the result returns.

The qualitative responses add the same message from another angle. Clinicians want clearer resistance mechanisms, better timing and standardization of molecular testing, stronger test-to-treatment links, and therapies with enough efficacy to make the molecular finding consequential.

For oncology, the emerging task is therefore to connect three advances that are often discussed separately: earlier recognition of resistance, more reliable interpretation of what changed, and a treatment portfolio broad enough to act on that information. The precision of the test matters. The precision of the next decision matters more.

Plan for progression before it happens
Preserve prior molecular results, likely resistance pathways, and testing options so the next work-up does not begin from zero.

Use retesting where actionability is plausible
Prioritize disease settings and treatment histories in which a new molecular result can reasonably alter sequencing or trial eligibility.

Make interpretation multidisciplinary when complexity rises
Molecular tumor-board or equivalent expertise can help align pathology, genomics, imaging, treatment evidence, and patient context.

Measure the value of testing by decisions changed
The important endpoint is not how much molecular information is generated, but whether the result supports a timely, evidence-based next step.

REFERENCES AND DATA SOURCE

Sources used for this report

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