

# Differences in historical operational biomarker positivity between two plasma-based comprehensive genomic profiling platforms in Japan: a nationwide C-CAT study

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## Research Article

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# Abstract

## Background

A nationwide study found a large historical difference in operational biomarker positivity between liquid comprehensive genomic profiling platforms. Whether case mix, calendar time, or facility composition explained it was uncertain.

## Methods

We analyzed 14,878 FoundationOne Liquid CDx (F1L) and 2,042 Guardant360 CDx (G360) records through March 31, 2025. The patient-level composite comprised seven prespecified biomarkers linked to approved therapies in Japan. Analyses included sequential adjustment, restriction to facilities using both platforms, and evaluation of tumor mutational burden-high (TMB-H).

## Results

Positivity was 14.323% (2,131/14,878) with F1L and 4.652% (95/2,042) with G360 (risk difference [RD], – 9.671 percentage points; 95% confidence interval [CI], – 10.744 to – 8.598). Patient-background- and calendar-adjusted positivity was 14.351% versus 4.498% (RD, – 9.853; 95% CI, – 11.087 to – 8.619). Across 171 both-platform facilities, the RD was – 10.233 (95% CI, – 11.586 to – 8.880). During the study period, TMB was not reported by the Japanese G360 configuration, and all G360 C-CAT TMB fields were blank. TMB-H alone occurred in 1,398 F1L-positive cases (65.6%); excluding TMB-H yielded an RD of – 0.384 (95% CI, – 1.420 to 0.652).

## Conclusions

Measured adjustment did not attenuate the historical contrast, which persisted in both-platform facilities. Its marked reduction after TMB-H exclusion identifies historical TMB reporting asymmetry as a major feature. Findings concern operationally available information, not comparative assay performance.

## Introduction

Comprehensive genomic profiling (CGP) supports precision oncology by providing biomarker information relevant to treatment selection. Plasma-based CGP offers a minimally invasive alternative when adequate tumor tissue is unavailable or impractical to test[1, 2]. Its real-world contribution depends not only on analytical detection but also on which clinically relevant biomarkers are included in the information reported for interpretation. Nationwide Center for Cancer Genomics and Advanced

Therapeutics (C-CAT) data integrate CGP reports with clinical information in Japan, enabling evaluation of this operational information yield[3].

A previous nationwide C-CAT analysis evaluated a prespecified set of seven treatment-relevant biomarkers and found substantially different operational positivity between FoundationOne Liquid CDx (F1L) and Guardant360 CDx (G360), approximately 14.3% versus 4.7%[4]. The candidates were selected for direct links to therapies approved in Japan, with emphasis on tumor-agnostic treatment eligibility. Exact BRAF V600E was retained because it identifies an approved treatment in colorectal cancer, although that indication is not strictly tumor agnostic. This clinically grounded definition was fixed before the present reanalysis.

Because the platform groups in the previous analysis were unpaired, differences in patient characteristics, tumor distribution, calendar time, and facility selection could have contributed to the crude platform-associated contrast. Moreover, a patient-level operational composite can reflect not only the occurrence of qualifying biomarkers but also the historically available reporting scope of each platform. The extent to which measured case mix, temporal implementation, facility composition, and individual biomarker components accounted for the observed contrast remained unknown.

We therefore examined whether the historical seven-candidate operational positivity difference was attenuated after sequential adjustment for measured patient characteristics and calendar time, evaluated its robustness after restriction to facilities using both platforms, and quantified the contributions of individual components to the observed contrast. The study was designed to evaluate operationally available biomarker information rather than comparative assay sensitivity or a causal platform effect.

## Methods

### Study design and data source

We conducted a nationwide, multicenter, retrospective observational study using case and CGP report data from the Japanese C-CAT database[3]. From the nationwide cohort used in the previous analysis, which included tissue- and plasma-based CGP, we selected patients tested with F1L[5] or G360[6] through March 31, 2025. The resulting historical liquid-CGP cohort comprised 16,920 patients: 14,878 tested with F1L and 2,042 with G360. Three whole-assay failures were retained in the denominator, consistent with the original operational comparison. The primary contrast was the between-platform difference in patient-level operational positivity.

### Historical operational positivity outcome

Historical operational positivity outcome

The primary outcome reproduced the previously published patient-level union of seven candidates selected for direct links to approved therapies in Japan: (1) microsatellite instability (MSI) high or equivocal; (2) TMB-H; (3) NTRK1, NTRK2, or NTRK3 fusion/rearrangement; (4) RET fusion/rearrangement; (5) ERBB2 amplification; (6) ALK fusion/rearrangement; and (7) exact BRAF V600E[4]. The set emphasized tumor-agnostic treatment eligibility; BRAF V600E was retained because of its direct link to an approved colorectal cancer treatment. Any qualifying candidate generated one composite event regardless of overlap. MSI equivocal was retained to reproduce the original operational definition and was not interpreted as confirmed MSI-high. Fusion/rearrangement candidates required the specified gene and change terms, ERBB2 required amplification, and BRAF required exact V600E after validated normalization. Detailed aliases and mapping are provided in Supplementary Methods and Table S1.

For F1L, TMB-H required a high status or, when status was blank, a numeric value of at least 10 mutations/Mb; a nonblank status took precedence. During the study period, TMB was not among the biomarkers reported by the Japanese G360 CDx configuration. At the introduction of G360 into C-CAT, official documentation stated that total TMB was displayed only for GenMineTOP, and the Japanese G360 package insert lists sequence alterations, amplifications, fusions, and MSI-High but not TMB[7, 8]. Consistently, numeric and categorical TMB fields were blank in all 2,042 G360 C-CAT records. These records were classified as having no available TMB information, not as TMB-low, TMB-negative, or 0% TMB-H positivity.

## Statistical analysis

The contrast was G360 minus F1L, with risk differences (RDs) in percentage points. Model 0 was crude. Model 1 used logistic regression with platform, continuous linear age, sex, and the prespecified 12-category tumor/organ group. Model 2 added calendar time from the case-layer registration date using a prespecified natural cubic spline with 4 degrees of freedom; its basis was fixed before outcome-model estimation.

For Models 1 and 2, platform-specific probabilities were obtained by marginal standardization (g-computation) over the relevant target population[9]. We report standardized probabilities, RDs, risk ratios, and 95% confidence intervals (CIs), with the RD as the principal contrast. Facility-cluster-robust sandwich variance addressed within-facility correlation but did not adjust for facility-level differences. No record lacked age, sex, tumor/organ group, registration date, or facility. Sequential changes in RDs were classified descriptively as attenuation, amplification, stability, or reversal and were not interpreted as causal proportions explained.

## Sensitivity and explanatory analyses

The both-platform sensitivity analysis was restricted to facilities contributing at least one record from each platform and applied the unchanged primary outcome and Model 2, including the fixed calendar

basis, with cluster-robust inference and standardization over the restricted cohort. This analysis assessed whether the primary finding depended on inclusion of platform-exclusive facilities; it did not constitute adjustment for facility-level factors.

Among F1L primary-positive records, TMB-H-positive cases were classified as TMB-H-only when all other six candidates were negative or as overlapping when at least one other candidate was positive. A supportive six-candidate union removed only TMB-H, retained the primary cohort and denominator, and applied Model 1 with marginal standardization and cluster-robust inference. The change in RD between outcome definitions was descriptive, not causal mediation or correction of the primary outcome. Detailed definitions are provided in Supplementary Methods; candidate-level counts and six-candidate raw event counts are reported in Supplementary Table S2.

## Ethics

Patients provided written informed consent before C-CAT registration. The Toyama University Institutional Review Board approved this secondary analysis on May 1, 2024 (R2024016), and the C-CAT Information Utilization Review Board approved it in August 2025 (CDU2025-010N). The study conformed to the 2013 revision of the Declaration of Helsinki.

## Results

### Study cohort and crude comparison

The selected liquid-CGP cohort included 16,920 patients from 267 facilities: 14,878 tested with F1L and 2,042 with G360. None was excluded for missing Model 1 covariates. The seven-candidate outcome occurred in 2,226 patients, reproducing the historical platform-specific numerators (Fig. 1 and Table 1). Positivity was 14.323% (2,131/14,878) with F1L and 4.652% (95/2,042) with G360. The crude RD was – 9.671 percentage points (95% CI, – 10.744 to – 8.598).

Table 1  
Patient and cohort characteristics by plasma-based CGP platform

| Characteristic                                                                                                                                                                                                                                                              | Overall       | F1L           | G360         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|---------------|--------------|
| Total patients, n                                                                                                                                                                                                                                                           | 16,920        | 14,878        | 2,042        |
| Contributing facilities, n                                                                                                                                                                                                                                                  | 267           | 266           | 172          |
| Patients in both-platform facilities, n (%)                                                                                                                                                                                                                                 | 13,559 (80.1) | 11,520 (77.4) | 2,039 (99.9) |
| Age at index report, years, median (IQR)                                                                                                                                                                                                                                    | 68 (59–74)    | 68 (59–74)    | 68 (60–75)   |
| <b>Sex, n (%)</b>                                                                                                                                                                                                                                                           |               |               |              |
| Man                                                                                                                                                                                                                                                                         | 9,704 (57.4)  | 8,569 (57.6)  | 1,135 (55.6) |
| Woman                                                                                                                                                                                                                                                                       | 7,216 (42.6)  | 6,309 (42.4)  | 907 (44.4)   |
| <b>Tumor/organ group, n (%)</b>                                                                                                                                                                                                                                             |               |               |              |
| Other                                                                                                                                                                                                                                                                       | 720 (4.3)     | 670 (4.5)     | 50 (2.4)     |
| Central/peripheral nervous system                                                                                                                                                                                                                                           | 95 (0.6)      | 90 (0.6)      | 5 (0.2)      |
| Breast                                                                                                                                                                                                                                                                      | 1,452 (8.6)   | 1,349 (9.1)   | 103 (5.0)    |
| Gynecologic                                                                                                                                                                                                                                                                 | 687 (4.1)     | 643 (4.3)     | 44 (2.2)     |
| Urinary tract                                                                                                                                                                                                                                                               | 2,675 (15.8)  | 2,540 (17.1)  | 135 (6.6)    |
| Liver                                                                                                                                                                                                                                                                       | 160 (0.9)     | 145 (1.0)     | 15 (0.7)     |
| Biliary tract                                                                                                                                                                                                                                                               | 1,986 (11.7)  | 1,727 (11.6)  | 259 (12.7)   |
| Thoracic                                                                                                                                                                                                                                                                    | 1,724 (10.2)  | 1,516 (10.2)  | 208 (10.2)   |
| Intestine                                                                                                                                                                                                                                                                   | 1,893 (11.2)  | 1,543 (10.4)  | 350 (17.1)   |
| Pancreas                                                                                                                                                                                                                                                                    | 4,459 (26.4)  | 3,707 (24.9)  | 752 (36.8)   |
| Head/neck and thyroid                                                                                                                                                                                                                                                       | 316 (1.9)     | 294 (2.0)     | 22 (1.1)     |
| Esophagus/stomach                                                                                                                                                                                                                                                           | 753 (4.5)     | 654 (4.4)     | 99 (4.8)     |
| <b>Registration year, n (%)</b>                                                                                                                                                                                                                                             |               |               |              |
| 2019                                                                                                                                                                                                                                                                        | 4 (< 0.1)     | 4 (< 0.1)     | 0 (0.0)      |
| 2020                                                                                                                                                                                                                                                                        | 18 (0.1)      | 18 (0.1)      | 0 (0.0)      |
| 2021                                                                                                                                                                                                                                                                        | 1,891 (11.2)  | 1,889 (12.7)  | 2 (0.1)      |
| 2022                                                                                                                                                                                                                                                                        | 4,043 (23.9)  | 4,038 (27.1)  | 5 (0.2)      |
| Data are n (%) unless otherwise indicated; percentages are calculated within columns. Registration year is based on the case-layer registration date. CGP, comprehensive genomic profiling; F1L, FoundationOne Liquid CDx; G360, Guardant360 CDx; IQR, interquartile range. |               |               |              |

| Characteristic                                                                                                                                                                                                                                                              | Overall        | F1L            | G360         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|----------------|--------------|
| 2023                                                                                                                                                                                                                                                                        | 4,302 (25.4)   | 3,916 (26.3)   | 386 (18.9)   |
| 2024                                                                                                                                                                                                                                                                        | 5,325 (31.5)   | 4,010 (27.0)   | 1,315 (64.4) |
| 2025                                                                                                                                                                                                                                                                        | 1,337 (7.9)    | 1,003 (6.7)    | 334 (16.4)   |
| Primary seven-candidate outcome, n (%)                                                                                                                                                                                                                                      | 2,226 (13.156) | 2,131 (14.323) | 95 (4.652)   |
| Data are n (%) unless otherwise indicated; percentages are calculated within columns. Registration year is based on the case-layer registration date. CGP, comprehensive genomic profiling; F1L, FoundationOne Liquid CDx; G360, Guardant360 CDx; IQR, interquartile range. |                |                |              |

Table 2  
Sequential estimates and both-platform facility sensitivity

| Analysis                                                                                                                                                                                                                                      | N      | Facilities / clusters | F1L, % | G360, % | RD, pp (95% CI)             | RR (95% CI)            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|-----------------------|--------|---------|-----------------------------|------------------------|
| Crude                                                                                                                                                                                                                                         | 16,920 | 267                   | 14.323 | 4.652   | -9.671 (-10.744 to -8.598)  | 0.325 (0.266 to 0.397) |
| Model 1                                                                                                                                                                                                                                       | 16,920 | 267                   | 14.313 | 4.600   | -9.713 (-10.914 to -8.512)  | 0.321 (0.259 to 0.399) |
| Model 2                                                                                                                                                                                                                                       | 16,920 | 267                   | 14.351 | 4.498   | -9.853 (-11.087 to -8.619)  | 0.313 (0.252 to 0.390) |
| Both-platform facilities: Model 2                                                                                                                                                                                                             | 13,559 | 171                   | 14.612 | 4.379   | -10.233 (-11.586 to -8.880) | 0.300 (0.240 to 0.375) |
| The contrast is G360 minus F1L; RD is the principal contrast and is reported in percentage points. Model-based values are marginal standardized probabilities; crude values are observed proportions.                                         |        |                       |        |         |                             |                        |
| All rows use the seven-candidate primary outcome. Model 1 included platform, continuous linear age, sex, and the prespecified 12-category tumor/organ group. Model 2 added calendar time as a natural cubic spline with 4 degrees of freedom. |        |                       |        |         |                             |                        |
| Facility-cluster-robust inference addressed within-facility correlation but did not adjust for facility-level differences. The both-platform analysis has a different target population and is not a within-facility comparison.              |        |                       |        |         |                             |                        |
| CI, confidence interval; F1L, FoundationOne Liquid CDx; G360, Guardant360 CDx; RD, risk difference; RR, risk ratio.                                                                                                                           |        |                       |        |         |                             |                        |

**Table 3.** TMB-H decomposition and six-candidate supportive analysis

**Panel A. TMB-H decomposition among F1L primary-positive cases**

| Item                                 | Count | % of F1L-positive cases |
|--------------------------------------|-------|-------------------------|
| F1L primary-positive cases           | 2,131 | 100.0                   |
| TMB-H positive                       | 1,681 | 78.9                    |
| TMB-H-only                           | 1,398 | 65.6                    |
| TMB-H overlapping ≥1 other candidate | 283   | 13.3                    |

#### Panel B. Seven-candidate and six-candidate Model 1 outcomes

| Outcome                                          | F1L standardized % | G360 standardized % | RD, pp (95% CI)               | Descriptive absolute RD reduction |
|--------------------------------------------------|--------------------|---------------------|-------------------------------|-----------------------------------|
| Seven-candidate primary outcome                  | 14.313             | 4.600               | -9.713<br>(-10.914 to -8.512) | Reference                         |
| Six-candidate supportive outcome excluding TMB-H | 4.941              | 4.556               | -0.384<br>(-1.420 to 0.652)   | 96.0%                             |

The six-candidate analysis is supportive and changes the outcome definition. The 96.0% reduction in the absolute Model 1 RD is descriptive and is not a causal decomposition or mediation estimate.

G360 TMB fields were data-layer unavailable during the study period; blank fields were not treated as TMB-low, TMB-negative, or 0% TMB-H positivity. Underlying G360 TMB-H status is unknown.

CI, confidence interval; F1L, FoundationOne Liquid CDx; G360, Guardant360 CDx; RD, risk difference; TMB-H, tumor mutational burden-high.

## Sequential adjustment

Model 1 included all 16,920 patients, all 2,226 events, and 267 facility clusters, with no complete-case exclusions. Standardized positivity was 14.313% with F1L and 4.600% with G360; the adjusted RD was -9.713 percentage points (95% CI, -10.914 to -8.512). Relative to the crude estimate, the RD changed by -0.042 percentage points and its absolute magnitude increased slightly. Thus, adjustment for measured patient background did not attenuate the contrast.

Model 2 added calendar time and was the final estimable sequential model, using the same 16,920 patients, 2,226 events, and facility clusters. Standardized positivity was 14.351% with F1L and 4.498% with G360, yielding an RD of -9.853 percentage points (95% CI, -11.087 to -8.619) (Table 2 and Fig. 2). The RD changed by -0.140 percentage points from Model 1 and by -0.182 from the crude comparison. Adding calendar time therefore did not attenuate the contrast. Supportive relative measures are reported in Table 2.

Across the sequential models, standardized F1L positivity remained near the crude proportion, whereas standardized G360 positivity remained below 5%. Neither adjustment step shifted the RD toward zero. The direction and magnitude of these estimates therefore provided a consistent measured-adjustment result, although Model 2 did not address unmeasured or facility-level confounding.

## **Both-platform facility analysis**

Of 267 facilities, 171 used both platforms. The restricted cohort included 13,559 patients (F1L, 11,520; G360, 2,039) and 1,767 events; it retained the primary outcome and Model 2 specification. Standardized positivity was 14.612% with F1L and 4.379% with G360, producing an RD of – 10.233 percentage points (95% CI, – 11.586 to – 8.880). The estimate had the same direction and an overlapping CI relative to full-cohort Model 2. Thus, the large contrast was retained after excluding platform-exclusive facilities, although the restriction changed the target population and did not eliminate facility-level confounding.

## **TMB-H and supportive outcomes**

Among 2,131 F1L-positive patients, 1,681 were TMB-H positive: 1,398 were TMB-H-only and 283 overlapped at least one other candidate (Table 3). Thus, TMB-H-only cases represented 65.6% of F1L-positive cases, and removal of TMB-H reduced the F1L event count by 1,398. During the study period, TMB was not included in the Japanese G360 reporting scope, and the numeric and categorical TMB fields were blank in all 2,042 G360 C-CAT records.

Under the supportive six-candidate outcome excluding TMB-H, the primary cohort and denominator were unchanged. Model 1 standardized positivity was 4.941% with F1L and 4.556% with G360. The adjusted RD was – 0.384 percentage points (95% CI, – 1.420 to 0.652). Compared descriptively with the seven-candidate Model 1 RD of – 9.713 percentage points, its absolute magnitude was 96.0% smaller. This comparison changed the outcome definition and was not a causal explanation, mediation proportion, or corrected primary outcome.

The six-candidate comparison was interpreted alongside the TMB-H-only and overlap decomposition. It quantified the residual platform-associated contrast after removing a component that was historically reported for F1L but not for G360 in Japan, rather than re-estimating the same primary endpoint under improved measurement.

## **Discussion**

This nationwide C-CAT study reproduced the large historical difference in seven-candidate operational positivity between F1L and G360. Adjustment for measured patient characteristics and calendar time did not attenuate the contrast, and a similarly large difference remained after restriction to 171 facilities using both platforms. By contrast, excluding TMB-H reduced the absolute Model 1 RD by 96.0%.

Together, these findings identify the historical difference in TMB reporting scope in Japan as a major feature of the observed platform-associated operational contrast.

The crude RD of – 9.671 percentage points changed only slightly to – 9.713 after patient-background adjustment and – 9.853 after adding calendar time. Standardized F1L positivity remained near 14%, whereas standardized G360 positivity remained below 5%. The stability of the contrast across these steps indicates that the measured differences in patient composition, tumor distribution, and temporal implementation did not account for the large historical difference.

Restriction to the 171 facilities that used both platforms yielded an RD of – 10.233 percentage points (95% CI, – 11.586 to – 8.880), with the same direction and a magnitude similar to the full-cohort Model 2 estimate. This supportive result shows that inclusion of platform-exclusive facilities alone did not account for the primary contrast.

The TMB-H decomposition provided the clearest explanation of the historical contrast. Of 2,131 F1L-positive patients, 1,398 were TMB-H-only (65.6%) and 283 had TMB-H overlapping another candidate. Removing TMB-H produced a six-candidate Model 1 RD of – 0.384 percentage points (95% CI, – 1.420 to 0.652), a descriptive 96.0% reduction in absolute magnitude from the seven-candidate Model 1 RD. During the study period, TMB was reported for F1L but not by the Japanese G360 configuration, consistent with C-CAT implementation documentation and the blank TMB fields observed in all G360 records[7, 8]. The convergence of the component decomposition and the six-candidate analysis shows how historical reporting scope shaped the treatment-relevant information available in routine care.

These results highlight reporting scope as an integral part of real-world CGP implementation. The information that reaches clinicians depends on both the molecular findings and the biomarkers included in the platform- and period-specific report[1–3]. Because TMB-H can inform tumor-agnostic therapeutic consideration[10], inclusion of TMB in clinical reporting can broaden the treatment-relevant information available for review. Comparative evaluation of CGP platforms should therefore account for the reporting configuration in use during the study period, and reporting scope should evolve with clinically relevant biomarkers and approved treatment options.

Strengths include the nationwide cohort across 267 facilities, reproduction of the published historical cohort and outcome, and a clinically grounded seven-candidate definition fixed before reanalysis. Sequential modeling separated measured patient-background and calendar adjustment, marginal standardization yielded interpretable absolute contrasts, and cluster-robust inference addressed within-facility correlation[9, 11]. The both-platform restriction tested a specific aspect of facility composition, and patient-level decomposition distinguished TMB-H-only from overlapping positivity while preserving the seven-candidate outcome as primary.

## Limitations

This study has limitations. The platform groups were unpaired, and measured covariates did not capture every determinant of platform selection, circulating tumor DNA yield, or opportunity to observe a qualifying result. Restriction to both-platform facilities changed the target population and did not eliminate selection or residual facility-level confounding. Accordingly, sequential changes in standardized RDs and the 96.0% reduction after TMB-H exclusion are descriptive rather than causal decomposition or mediation estimates. The comparison reflects historical operationally available information, not biological prevalence, assay sensitivity, diagnostic accuracy, or intrinsic assay performance. Because TMB was not reported by the Japanese G360 configuration during the study period, underlying TMB-H status could not be determined for G360-tested patients, and blank TMB fields should not be interpreted as TMB-low or negative. MSI equivocal was retained to reproduce the historical operational definition and was not interpreted as confirmed MSI-high. We did not evaluate whether reported information led to a recommendation, treatment, or clinical benefit. Finally, the March 31, 2025 data cutoff and the evolving nature of reporting configurations limit direct extrapolation to current or future platform specifications.

## Conclusion

The large historical difference in seven-candidate operational positivity was not explained by measured patient background, calendar time, or inclusion of platform-exclusive facilities, but became markedly smaller after TMB-H was excluded. Historical TMB reporting asymmetry was therefore a major feature of the observed contrast. These findings underscore that the reporting scope in use at a given time materially shapes the treatment-relevant information available from CGP in routine clinical practice.

## Declarations

**Conflict of interest:** SK reports lecture honoraria from Daiichi Sankyo Co., Ltd. and stock ownership in Daiichi Sankyo Co., Ltd. and Ono Pharmaceutical Co., Ltd., all outside the submitted work. All other authors declare no relevant financial or non-financial interests.

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**Authors' contributions:** SK conceived the study. SK curated data. SK contributed to data acquisition and interpretation. SK performed the analyses and drafted the manuscript. NN and RH provided critical revisions. All authors read and approved the final manuscript.

**Ethics Approval:** This study used anonymized data derived from the C-CAT database. Under the Japanese cancer genomic medicine system, patients provide informed consent before registration in C-CAT. The present secondary analysis used anonymized aggregated data obtained through the C-CAT data-use framework and was conducted in accordance with the governance framework for secondary use of C-CAT data in Japan. This secondary analysis was approved by the Institutional Review Board of Toyama University on May 1, 2024 (Approval No. R2024016) and the Information Utilization Review

Board of C-CAT in August 2025 (Approval No. CDU2025-010N). The study was conducted in accordance with the Declaration of Helsinki, as revised in 2013.

The anonymized aggregated C-CAT data were accessed for research purposes on 29 January 2026.

The authors did not have access to information that could identify individual participants during or after data collection.

**Consent to participate:** Under the Japanese cancer genomic medicine system, written informed consent was obtained before registration in C-CAT.

**Consent for publication:** Not applicable (no individual identifying data are included).

**Data availability:** The authors do not control the underlying C-CAT database. The data used in this study were obtained as anonymized aggregated counts through the approved C-CAT data-use framework and are subject to institutional and data-provider governance restrictions. Therefore, the underlying source-level C-CAT data are not publicly available from the authors. Access to source-level C-CAT data requires formal application to C-CAT and the relevant institutional approvals under the Japanese cancer genomic medicine governance framework.

**Generative AI use:** During the preparation of this manuscript, the authors used ChatGPT (OpenAI) as AI-assisted tools to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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## Figures

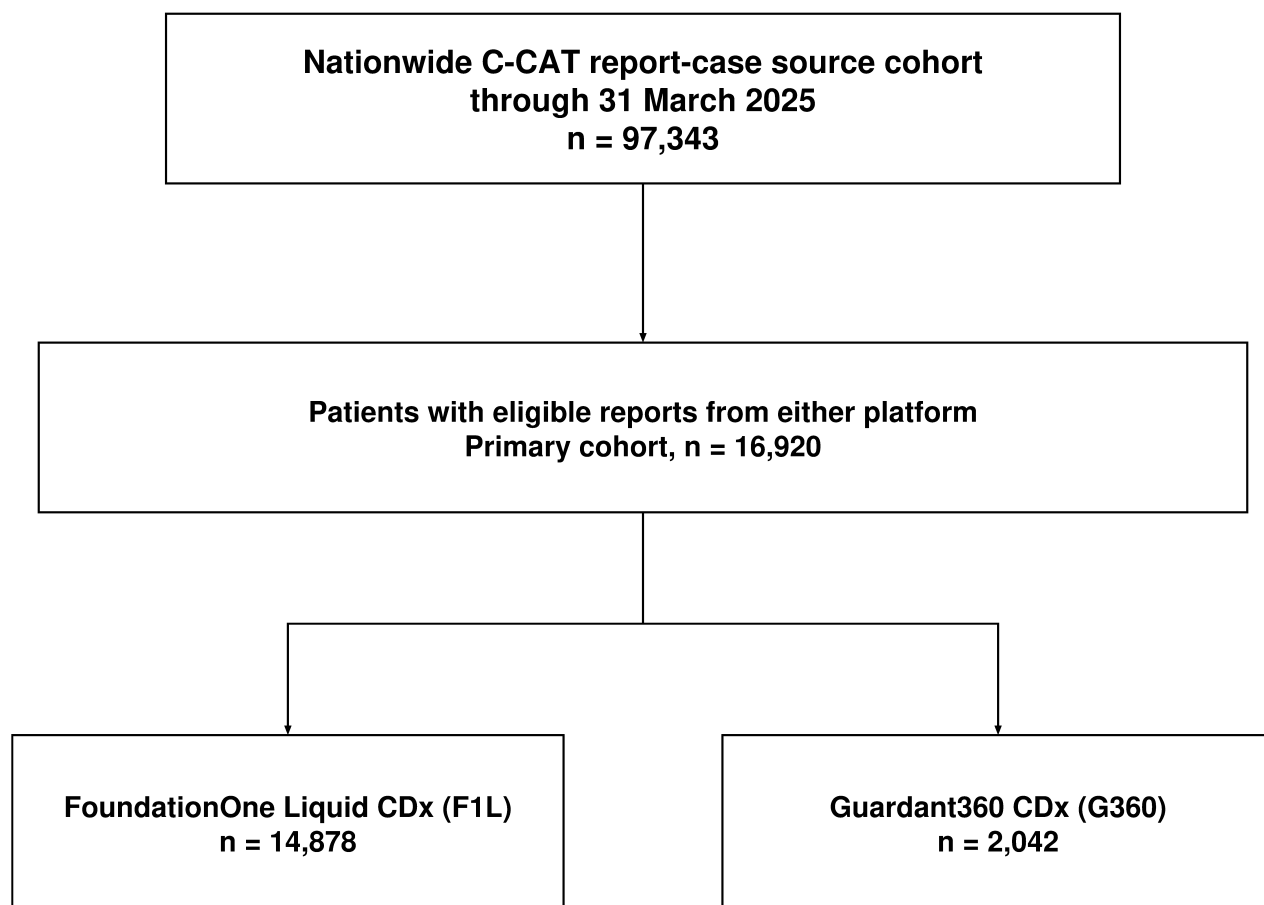


**Figure 1**

Study cohort. The flow diagram shows selection of the primary historical liquid comprehensive genomic profiling cohort from the nationwide Center for Cancer Genomics and Advanced Therapeutics (C-CAT) report-case source cohort. The nationwide source cohort comprised 97,343 records through 31 March 2025. From this source, 16,920 eligible patients tested with FoundationOne Liquid CDx (F1L; n=14,878) or Guardant360 CDx (G360; n=2,042) were included. The cohort comprised 267 facilities and 2,226 patient-level seven-candidate historical operational-positivity events. Three F1L whole-assay failures were retained in the denominator to reproduce the historical operational comparison. The prespecified primary and both-platform-facility analyses are reported in Table 2, whereas the TMB-H decomposition and six-candidate model estimates are reported in Table 3; candidate-level counts are provided in Supplementary Table S2 rather than as additional branches in this patient-selection flow. CGP, comprehensive genomic profiling; TMB-H, tumor mutational burden-high

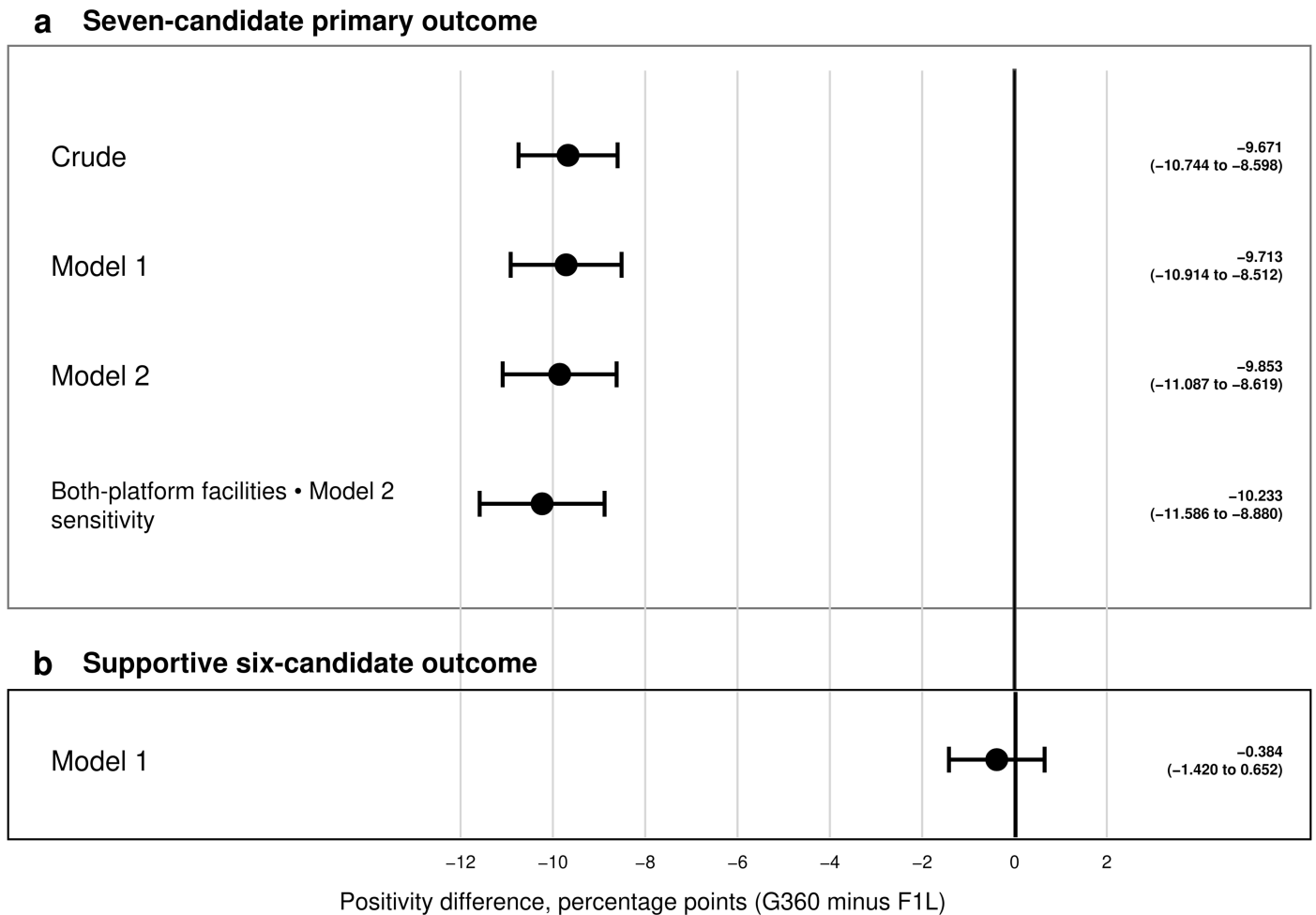


**Figure 2**

Risk differences in historical operational biomarker positivity. The forest plot reports risk differences (RDs; G360 minus F1L) in percentage points with 95% confidence intervals (CIs); the vertical reference line is zero. Negative values indicate lower historical operational positivity with G360 relative to F1L, and positive values indicate higher operational positivity. Panel a presents the seven-candidate primary outcome in the full cohort for the crude analysis (RD, -9.671; 95% CI, -10.744 to -8.598), Model 1 (RD, -9.713; 95% CI, -10.914 to -8.512), and Model 2 (RD, -9.853; 95% CI, -11.087 to -8.619), followed by the both-platform-facility sensitivity analysis using the unchanged Model 2 (RD, -10.233; 95% CI, -11.586 to -8.880). This sensitivity analysis was restricted to patients tested at the 171 facilities that used both platforms; the estimate therefore pertains to this restricted target population. Model 1 included platform, continuous linear age, sex, and the prespecified 12-category tumor/organ group; Model 2 added calendar time as a natural cubic spline with 4 degrees of freedom. Model-based probabilities were marginally standardized over the relevant target population with facility-cluster-robust inference, which addressed within-facility correlation but did not adjust for facility-level differences. Panel b presents the supportive

six-candidate outcome excluding TMB-H in the full cohort using Model 1 (RD, -0.384; 95% CI, -1.420 to 0.652). The six-candidate outcome is supportive and is not part of the primary sequential hierarchy. G360 TMB fields were data-layer unavailable during the study period; blanks were not treated as TMB-low, negative, or 0% TMB-H positivity, and underlying G360 TMB-H status is unknown. F1L, FoundationOne Liquid CDx; G360, Guardant360 CDx; TMB-H, tumor mutational burden-high

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [49Supplementary20260803d.docx](#)