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A process to reanalyze clinical DNA sequencing data for biomarker matching in the Lung-MAP Master Protocol

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Abstract

For cancer clinical trials that require central confirmation of tumor genomic profiling, exhaustion of tissue from standard-of-care testing may prevent enrollment. For Lung-MAP, a master protocol that requires results from a defined centralized clinical trial assay to assign patients to a therapeutic substudy, we developed a process to repurpose existing commercial vendor raw genomic data for eligibility: genomic data reanalysis (GDR). Molecular results for substudy assignment were successfully generated for 369 of the first 374 patients (98.7%) using GDR for Lung-MAP, with a median time from request to result of 9 days. During the same period, 691 of 791 (87.4%) tissue samples received successfully yielded results, in a median of 14 days beyond sample acquisition. GDR is a scalable bioinformatic pipeline that expedites reanalysis of existing data for clinical trials in which validated integral biomarker testing is required for participation.

Key words. Lung-MAP; genomic profiling; clinical trial; eligibility; biomarker.

Introduction

The widespread availability of DNA comprehensive genomic profiling (CGP) for advanced solid tumors has catalyzed the identification of patient populations with molecularly defined cancer types for enrollment in clinical trials of precision therapies.[1,2] However, variable analytic performance and biomarker definitions across commercially available assays, especially for nuanced or complex biomarkers, can lead to undesired variability in the enrolled population.[3] Many clinical trials therefore use a predefined clinical trial assay (CTA) for screening to identify a consistent biomarker-positive population.[4] This is problematic for patients who have already completed routine clinical testing indicating potential eligibility. Confirmatory CTA testing can cause significant delays in tissue acquisition, tissue availability, or repeat testing.[5]

Lung-MAP is a master protocol that uses a defined CTA for centralized tumor CGP to assign patients with previously treated non–small cell lung cancer to a Lung-MAP substudy based on genomics.[6,7] Increasingly, patients being evaluated for participation in Lung-MAP already had CGP using the same commercial platform as the CTA.

We developed a pipeline for genomic data reanalysis (GDR) for Lung-MAP where existing raw genomic data from the same commercial assay were reanalyzed for Lung-MAP. Because analysis for commercial and research samples uses the same sequencing data to generate different reports, we hypothesized that reuse of existing results to generate CTA reports could accelerate trial eligibility and enrollment. Here we describe the workflow for rapid reanalysis of existing CGP data to expedite participation in a Lung-MAP substudy and avoid retesting tissue.

Methods

From January 28, 2019 through December 2023, the CTA for Lung-MAP has been CGP testing by FoundationOne CDx.[8] GDR was introduced in April 2021, and then opened to all Lung-MAP study sites in June 2021. Sites submitted a request for reanalysis using the SWOG Specimen Tracking System (also used for tissue submissions). This system delivered the request to the central laboratory (Foundation Medicine). Upon completion of reanalysis the results were reported to the SWOG Statistics and Data Management Center (SDMC) which notified sites of the patient's substudy assignment. This involved coordination between sites conducting Lung-MAP, the central laboratory, and the SWOG SDMC (Figure 1A).

Requests for reanalysis were allowed for previous CGP results completed on or after September 1, 2019. Results were reanalyzed with the current bioinformatic pipeline used for standard-of-care CGP.[8] Results were then used to populate draft GDR-generated reports, which were compared to the original report for agreement. Any discrepancies were resolved by expert FMI review prior to release to investigators. GDR results were then provided to the coordinating center to inform eligibility for substudies.
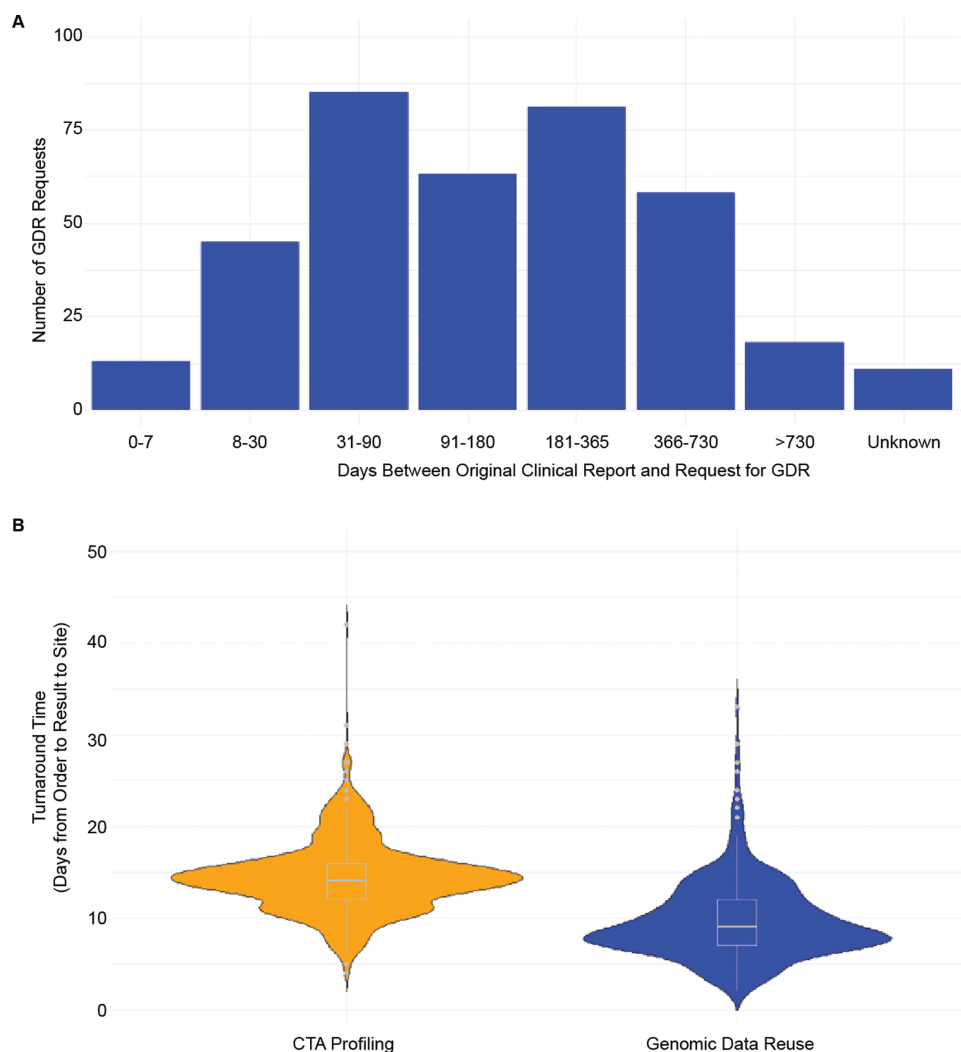
Results

From May 14, 2021 to September 30, 2023, tissue was submitted for analysis for 791 patients and requests for reanalysis were submitted for 374 patients. Thirty-two percent of screening registrations to Lung-MAP over this time were via GDR (Figure 1B).

Requests for GDR were initiated after a broad range of intervals after delivery of the original report (median: 147 days, range: 0-1, 202, interquartile range [IQR]: 54-337; Figure 2A). The turnaround time (TAT) from the request by
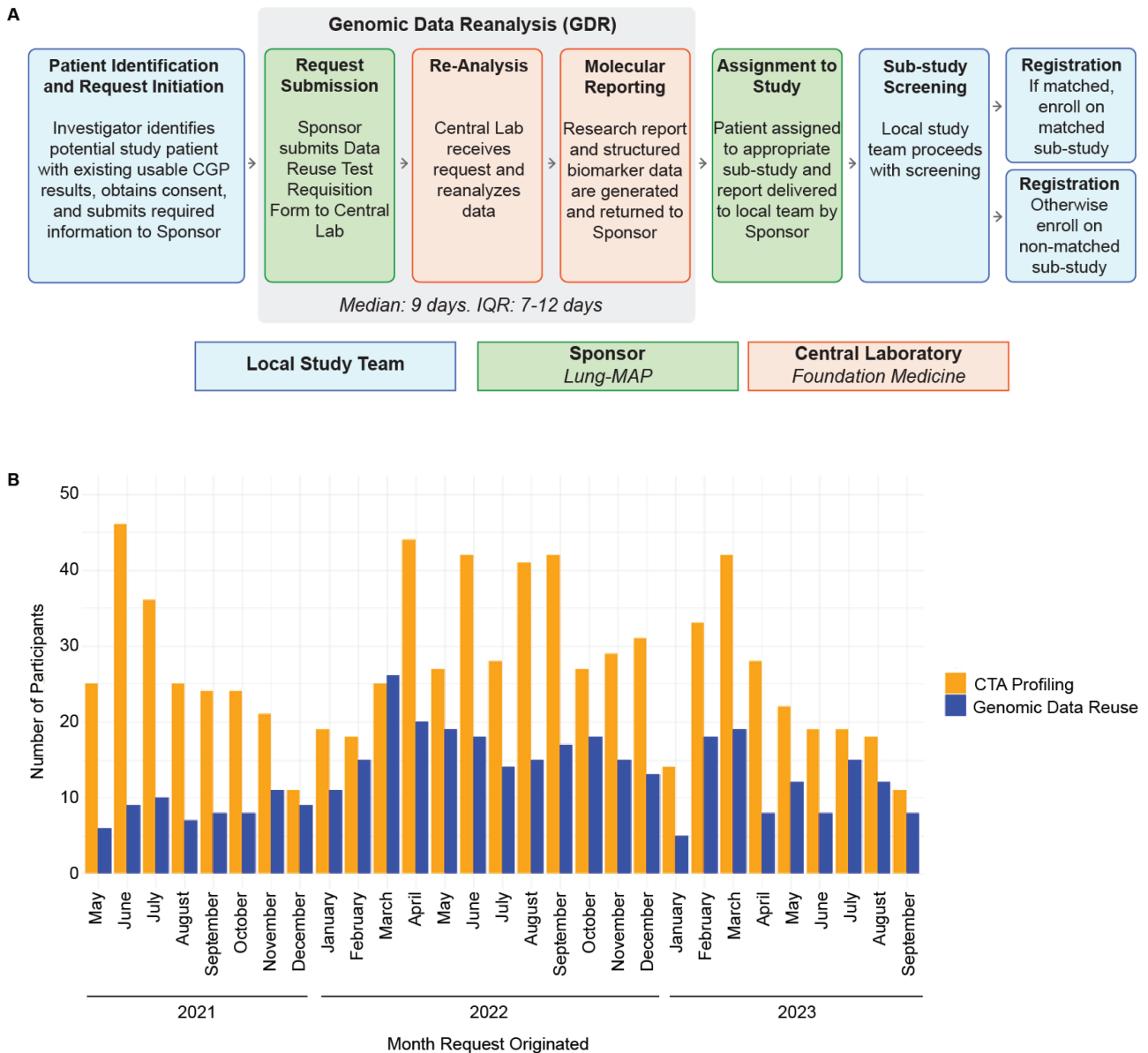
Figure 1. Genomic data reuse (GDR) process overview and uptake. (A) Flowchart illustrating interactions between local study team, sponsor, and central laboratory. (B) Uptake of the GDR process by month as compared to sample profiling.

Figure 2. Metrics of genomic data reuse (GDR) process. (A) Distribution of intervals from sign-out of the source report to request for GDR. (B) Time from tissue submission or request for GDR to return of result to site.

investigators to communication back to the site for substudy assignment was a median of 9 calendar days (range: 2-33, IQR: 7-12; Figure 2B). Cases taking >10 days were typically a result of needing additional communication with the site to confirm a change in diagnosis from the original report. In contrast, the median TAT for CTA profiling was 14 days (range: 4-42; IQR: 12-16). This difference was statistically significant ($P < .001$).

Reanalysis was successful for 369/374 patients (98.7%). The 5 cases where GDR was unable to produce usable results were due to various reasons including: the previous test was not FoundationOne CDx (3 cases), the previous test was not for NSCLC (1 case), and the previous test should not have successfully produced results (1 case). For on-study tissue analysis, there were 691 successful cases (87.4%). For the 100 (12.6%) that were not able to produce useable CGP results, the reasons for unsuccessful CGP were insufficient DNA or low DNA yield ($n = 77$), insufficient tumor size ($n = 13$), unsuccessful sequencing ($n = 1$), and unsuccessful for other reasons ($n = 21$). CGP could have been unsuccessful for multiple reasons.

GDR utilizes updated bioinformatic methods incorporating recent advances in scientific knowledge, which can introduce discrepancies with the original report. Three original reports were amended due to updates in genomic information identified during GDR, respectively due to a newly identified *TP53* copy number loss, a reclassification of a complex rearrangement involving *TP53*, and a newly identified *STK11* copy number loss.

Discussion

Reanalysis of CGP data enables the efficient reuse of prior standard-of-care results for clinical trial screening while conserving tissue without compromising quality. We demonstrate that the median TAT of GDR is 5 days faster than for tissue-based CGP, on top of other potential delays in tissue procurement. GDR is also highly reliable in producing evaluable results, with almost all GDR requests producing results versus 87% of research CGP requests. This is the first description of reanalysis of CGP data to our knowledge for clinical trial eligibility. This process is generalizable to any CGP test, including liquid biopsy, and is currently being considered for other clinical trials beyond Lung-MAP.

Limitations to GDR include requiring the clinician to be aware of prior testing results and to gather patient consent for GDR. The burden imposed by these requirements, especially when patients are treated by multiple oncologists, is

potentially addressable by increasing convenient electronic access to prior testing results with electronically obtained consent as permissible. Additionally, some clinical scenarios require new CGP, such as to identify acquired resistance to prior targeted therapy, precluding the applicability of GDR. Finally, raw sequencing data information is not currently "portable" between CGP platforms, and sequencing platforms are not identical in scope and performance, precluding reanalysis of other sequencing results with a standardized bioinformatic platform. Reanalysis of CGP results from the plethora of platforms will likely require manual expert review of commercial reports, which could lower quality and enable little automation of study assignment, unlike GDR. For some trials with straightforward biomarker inclusion criteria, this may be solved by depositing structured results from multiple labs into a single harmonized database for querying. This proposed solution motivates the development of harmonization standards.

In the future, GDR may be applicable beyond clinical trial selection. A similar process could support companion diagnostic development, particularly in patients lacking additional tissue but with prior clinical results available for reanalysis. Overall, the results presented here demonstrate the efficiency of reanalyzing existing sequencing data for clinical trial assignment, thereby facilitating enrollment and establishing a new pathway for trial screening.

Author contributions

J.W.N.: Conception/design, Provision of study material or patients, Manuscript writing, Final approval of manuscript. K.M.: Collection and/or assembly of data, Data analysis and interpretation. R.B.: Collection and/or assembly of data. R.S.P.H.: Conception/Design. M.C.H.: Conception/Design. C.A.: Collection and/or assembly of data, Data analysis and interpretation. J.P.: Conception/design, Provision of study material or patients. R.H.: Conception/design, Provision of study material or patients. K.L.R.: Provision of study material or patients. H.B.: Provision of study material or patients. L.H.: Collection and/or assembly of data. M.W.R.: Collection and/or assembly of data, Data analysis and interpretation, Manuscript writing, Final approval of the manuscript. L.W.P.: Conception/design, Data analysis and interpretation, Manuscript writing, Final approval of the manuscript. D.E.K.: Conception/design, Provision of study material or patients, Final approval of manuscript.

Conflicts of interest

J.W.N.: Honoraria: CME Matters, Clinical Care Options CME, Research to Practice CME, Medscape CME, Biomedical Learning Institute CME, MLI Peerview CME, Prime Oncology CME, Projects in Knowledge CME, Rockpointe CME, MJH Life Sciences CME, Medical Educator Consortium, HMP Education. Consulting or Advisory Role: AstraZeneca, Genentech/Roche, Exelixis, Takeda Pharmaceuticals, Eli Lilly and Company, Amgen, Iovance Biotherapeutics, Blueprint Pharmaceuticals, Regeneron Pharmaceuticals, Natera, Sanofi/Regeneron, D2G Oncology, Surface Oncology, Turning Point Therapeutics, Mirati Therapeutics, Gilead Sciences, AbbVie, Summit Therapeutics, Novartis, Novocure, Janssen Oncology, Anheart Therapeutics. Research Funding: Genentech/Roche

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Data availability

The data underlying this article cannot be shared publicly to protect the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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