Clinical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

TARGET National: A UK-wide Liquid-based Molecular Profiling Programme
On Behalf of the TARGET National Consortium

A. Ortega-Franco [*], E. Darlington [*], A. Greystoke [†‡], M.G. Krebs [*§]

[*] The Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
[†] Translational and Clinical Research Institute, NU Cancer, Newcastle University, Newcastle upon Tyne, UK
[‡] Northern Centre for Cancer Care, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[§] Division of Cancer Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK

Keywords: Early phase clinical trial; ctDNA; Genomic profiling; Liquid biopsy; Precision medicine; Targeted therapy

Over the last two decades, oncology research has been focused on deciphering the biological processes responsible for cancer development and growth, with the promise of finding targetable molecular vulnerabilities [1]. The historical 'one size fits all' approach to cancer treatment based on tumour histology alone is associated with limited efficacy and a major focus of modern drug development is directed towards precision medicine, targeting treatments towards key molecular drivers [2,3]. In recent years, a growing body of targeted drugs have successfully entered the clinic, such as ROS1 [4,5] and KRAS G12C [6] inhibitors for lung cancer, spurred by rapid advances in sequencing technologies that enable the identification of oncogenic variants.

Most precision medicine clinical trials have focused on tissue-based assays to screen cancer patients for a panel of genomic variants amenable to experimental and/or approved targeted therapies [7–14]. Typically, next generation sequencing (NGS) assays are used as the most cost-effective approach to screen for a range of genetic alterations, maximising use of available tissue. In patients receiving targeted treatment based on profiling findings (i.e. 'matched' therapy), modest improvements in response rates, progression-free and/or overall survival have been achieved [7–14], but the highest benefit is consistently seen in those patients with definitive clonal driver alterations matched to selective targeted pathway inhibitors. As an exemplar, response rates to agents such as alectinib [ALK tyrosine kinase inhibitor (TKI)] in *ALK*-rearranged lung cancer are as high as 83% [15]. In EGFR mutant patients, osimertinib (EGFR-TKI) has shown a 71% response rate with a hazard ratio for progression-free survival of 0.30, compared with platinum-based chemotherapy [16]. An additional benefit of selecting patients for targeted therapies is to spare treatment toxicity to those unlikely to derive benefit.

An increasing number of genetic alterations are also seen across multiple disease types, so-called tumour agnostic alterations, such as *NTRK* rearrangements resulting in activating *NTRK* fusions. These occur in <1% of cancers overall (albeit more frequently in a small number of rare cancers) and as a recognised clonal driver, response rates to TRK TKIs across disease types are >60% [17–19]. We must, therefore, broaden access to cost-effective sequencing as a routine diagnostic across cancer types to maximise precision medicine opportunities for our patients.

The use of tissue-based assays in precision medicine trials is inherently limited and increases risk and burden for cancer patients. There are often challenges with insufficient or poor-quality tissue resulting in failed analysis, and delays in obtaining samples can lead to slow turnaround times, risking patient deterioration before a result is obtained. Furthermore, testing is often carried out on samples that can be months or even years old, giving inadequate representation of genomic variants that may have developed during the course of disease secondary to drug pressures and clonal evolution [20]. In addition, tissue samples depict only the mutations in a defined area of a single tumour site,

Author for correspondence: M.G. Krebs, Division of Cancer Sciences, The University of Manchester, c/o Clinical Research Facility, The Christie NHS Foundation Trust, 550 Wilmslow Road, Manchester, M20 4BX, UK.
E-mail address: matthew.krebs@manchester.ac.uk (M.G. Krebs).

https://doi.org/10.1016/j.clon.2022.10.005

Please cite this article as: Ortega-Franco A et al., TARGET National: A UK-wide Liquid-based Molecular Profiling Programme, Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.005

hence intra- and intertumoural heterogeneity is poorly represented [21].

In this context, the use of blood-based (liquid) biopsies, in particular circulating tumour DNA (ctDNA), has emerged as a promising tool for genomic analysis. Our original TARGET (Tumour Characterisation to Guide Experimental Targeted Therapy) trial was one of the first studies to capitalise on the use of ctDNA analysis to guide targeted experimental cancer therapies [22]. Patients with advanced solid cancer referred to the Experimental Cancer Medicine Team at the Manchester Cancer Research Centre for early phase clinical trials were offered ctDNA NGS testing using an in-house targeted sequencing panel to detect mutations in 641 cancer-associated genes. Data from the first 100 patients (TARGET Part A) demonstrated identification of actionable mutations in 41% patients; of whom 11% received a matched therapy. In addition, analysis of matched tissue samples showed good concordance between the tissue and blood-based assays in keeping with other studies [23–25]. These results support the use of minimally invasive liquid biopsies for comprehensive genomic profiling, with the additional advantage of ease of sampling, quicker turnaround compared with tissue-based testing and representation of the mutational landscape across all disease sites [20]. Notably, the analysis from the remaining 420 patients (TARGET Part B), to assess the clinical utility of ctDNA profiling, is currently ongoing. Notwithstanding, ctDNA is not detectable in all patients with differences in prevalence across disease types and tumour burden [20,26], thus tissue-based testing will still play an important and complementary role. Our intention is to broaden the access to liquid-based molecular profiling for patients and harness expertise across the UK early phase trial community for identification of suitable clinical trials to enhance matching rates.

Trial Design

TARGET National is a multicentre translational study to establish a national framework to offer molecular profiling from blood (or tissue) samples for patients being considered for early phase clinical trials across the Experimental Cancer Medicine Centre (ECMC) network in the UK (Figure 1). As of July 2022, TARGET National is open for recruitment in nine ECMCs and will expand rapidly to open at all adult centres across the country to recruit 6000 patients over a 5-year period.

Eligible patients should provide written consent, have histologically confirmed diagnosis of advanced solid cancer, be $\geq$16 years of age and fit enough to receive an experimental therapeutic agent. Patients will be expected to have received at least one prior line of therapy (but any line of treatment is permitted). Importantly, eligible patients must not currently be receiving systemic anti-cancer treatment (due to the potential impact on ctDNA analysis), unless the patient has clear evidence of progression on hormone-based therapies or TKIs. To ease trial access, cancer patients treated across the UK are encouraged to be referred through to any of the participating sites.

The main focus of TARGET National is genomic profiling via ctDNA due to ease of acquisition but investigators will have the option to submit tumour tissue if this is considered more appropriate, such as in cases of low tumour burden or cancers, such as sarcoma, where ctDNA levels are often lower [27]. Up to 60 ml of blood can be drawn from consented patients, but initially two tubes of 8.5 ml will be acquired for ctDNA analysis with Foundation One® Liquid CDx. This is a comprehensive NGS assay that covers 324 cancer-related genes for somatic point mutations, indels, copy number changes and fusions and two genomic signatures: tumour mutational burden and microsatellite status. The test requires the input of $\geq$25 nanograms DNA, further technical specifications can be found on the Foundation Medicine website [28]. Results will be turned around within 14 days and then discussed in a national molecular tumour board (MTB), where requested.

Relevant clinical data (including patients' demographics, previous therapies and family history) will be collected in a MACRO database developed and managed by Liverpool Clinical Trials Centre. For patients matched to an experimental treatment, data on tumour response and progression-free survival on matched treatment will also be collected. The consolidated dataset including genomic and associated clinical data will be made available through public repositories at the end of the study, creating a unique and valuable resource for the cancer research community. All patients will be consented to sharing of their pseudo-anonymised clinical genomic data.

Anonymised clinical data and raw genomic data will be uploaded to eTARGET [29], a bespoke digital solution, developed by digital the Experimental Cancer Medicine Team in Manchester and now available open source. This cloud-based software tool integrates clinical and genomic sequencing data, to facilitate a virtual national MTB discussion. Not all patient results will be discussed in the MTB due to capacity, but investigators will have the option to refer any cases where there is uncertainty regarding the findings/interpretation of results. This fortnightly meeting consisting of clinicians, biologists, clinical and translational scientists and bioinformaticians, reviews sequencing results and provides feedback to referring clinicians and patients regarding any 'actionable' alterations and/or any known available clinical trials (supported by trial finding software). In addition, the national MTB will give its recommendation for the need for confirmation and/or the disclosure of incidental germline findings. MTB outcomes are recorded in eTARGET, accessible to all investigators through secured access, and reports can be exported and uploaded to local electronic patient records.

Unlike local tumour boards, the national MTB sits in a unique position within the ECMC network, to access the collective expertise of professionals across the country and promote referrals between centres for available trials. Moreover, it provides a national platform to discuss and learn the clinical interpretation of complex genomic readouts and help to train oncologists in the rapidly advancing field of genomics and precision medicine.

Please cite this article as: Ortega-Franco A et al., TARGET National: A UK-wide Liquid-based Molecular Profiling Programme, Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.005

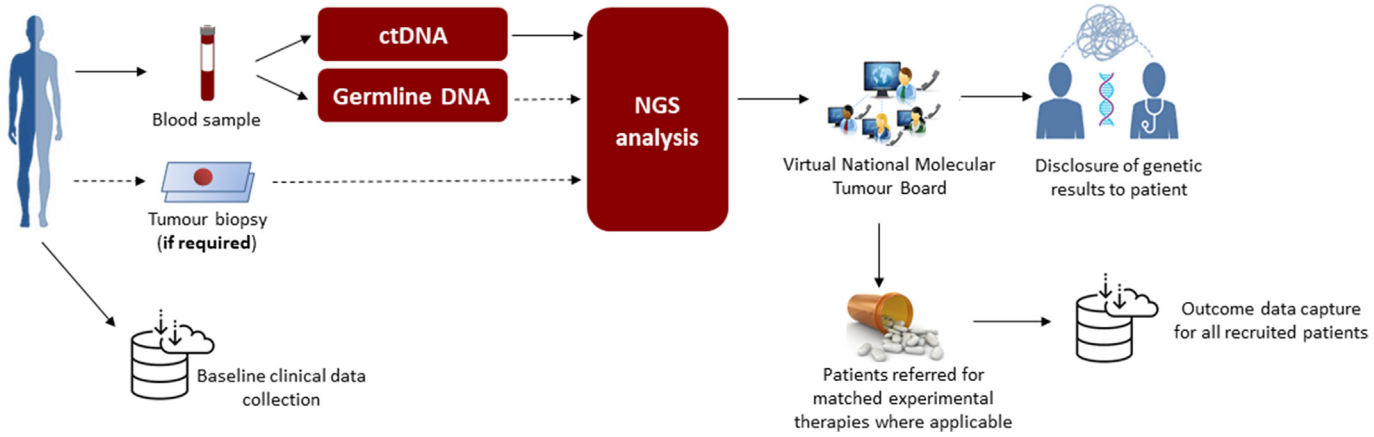

Fig 1. TARGET National trial schema.

The main risks for study participants are complications related to blood and (if required) tissue sampling. Data concerning incidental germline findings might cause distress to patients and their families. To minimise this risk, participants will have the option to opt out from receiving this information at consent. Patients deemed eligible for matched experimental therapies will be referred through to a recruiting site for further evaluation and discussion regarding the relevant trial.

Delivery of the TARGET National programme requires considerable resources, including clinical trial coordination support, ethical and regulatory processes, management of databases, investigator time for MTB discussion and feedback of results to patients, software solutions for clinical genomic data integration and maintenance, cost of NGS assays and bioinformatics support, coordination of sample acquisition/shipping and project management.

TARGET National: Vision and Potential Impact

TARGET National will fundamentally enhance opportunities and expand the reach for patients to participate in early phase trials of molecularly targeted cancer therapy trials in the UK.

By using a liquid-based broad NGS panel, we will be able to interrogate simultaneously a wide range of genomic alterations, thus reducing sequencing costs and enhancing opportunities for trial recruitment. The strong collaborations between the ECMC network will facilitate access to early phase clinical trials and reduce nationwide disparities in access to molecular profiling. Importantly, TARGET National complements the strategic approach of the NHS England Genomic Medicine Service to provide equitable access to genomic testing. The Genomic Medicine Service is currently focused on tissue-based testing aligned to the national genomics test directory for specific indications with associated reimbursed therapies as part of standard-of-care guidelines [30]. TARGET National complements this endeavour through provision of liquid biopsy and broad panel genomic testing in a population of patients considered fit enough for early phase clinical trials.

TARGET National will serve as the first national registry to capture the molecular characteristics of the early phase oncology population in the UK and the clinical outcome of patients treated with matched therapies. In addition, it will provide an important evidence base for the clinical utility of ctDNA (e.g. in which disease types it is most informative, frequency and prevalence of mutations detected and treatment response according to ctDNA matching) to help support the uptake of liquid biopsies in standard National Health Service practice.

The TARGET National protocol also incorporates flexibility to include additional assays from new commercial or academic partners, as technologies evolve (transcriptomic/metabolomic/immune biomarkers), with the advantage of being readily deployed across the entire ECMC network. The study provides an attractive infrastructure for identifying patients with molecular alterations for early phase trials and may promote new pharmaceutical partnerships for drug development programmes of novel precision medicines in the UK. The infrastructure also permits acquisition of additional samples for translational research models (i.e. cell cultures and animal models) and multi-omic analysis. This integrative approach could potentially provide information about as yet unknown genes or pathways important in cancer biology.

Conclusion

TARGET National is a unique endeavour in its scale to improve the access to liquid-based genomic testing for cancer patients across the country and by identifying patients for molecularly targeted treatments, expanding the access to clinical trials and its educational value in training the next generation of oncologists in clinical application of cancer genomics. eTARGET will serve as an interrogatable database for genomic alterations in the UK, enhancing our ability to identify rare variants, increasingly required in early phase trials of novel agents targeting rare populations.

Please cite this article as: Ortega-Franco A et al., TARGET National: A UK-wide Liquid-based Molecular Profiling Programme, Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.005

The flexible protocol for inclusion of emerging technologies opens the door for future collaborators to build on this infrastructure and maximise opportunities for patient access to trials.

Author Contributions

AO-F, ED, AG and MGK were responsible for manuscript preparation and editing.

Conflicts of Interest

M.G. Krebs reports financial support and equipment, drugs, or supplies were provided by F Hoffmann-La Roche Ltd. M.G. Krebs reports a relationship with F Hoffmann-La Roche Ltd that includes: consulting or advisory, funding grants, and speaking and lecture fees. M.G. Krebs reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory and speaking and lecture fees. M.G. Krebs reports a relationship with BerGenBio ASA that includes: consulting or advisory, funding grants, and travel reimbursement. M.G. Krebs reports a relationship with Immutep that includes: travel reimbursement. M.G. Krebs reports a relationship with OM Pharma Ltd that includes: consulting or advisory. M.G. Krebs reports a relationship with Seagen Inc that includes: consulting or advisory. M.G. Krebs reports a relationship with AstraZeneca Pharmaceuticals LP that includes: speaking and lecture fees. M.G. Krebs reports a relationship with Guardant Health Inc that includes: consulting or advisory. A. Greystoke reports consultancy/speaker fees from Foundation Medicine (Roche); consultancy fees from Guardant Health, Inc.

Acknowledgements

This study is funded by The Christie Charity, The Sir Bobby Robson Foundation and provision of Foundation Medicine genomic profiling services from Roche Products Limited, UK. We would like to acknowledge support from The Wibbersley and Thorne Society, The Experimental Cancer Medicine Network, the TARGET National Consortium and participating centres, National Institute for Health Research (NIHR) Manchester Biomedical Research Centre, NIHR Manchester Clinical Research Facility at The Christie and NIHR Clinical Research Facilities at participating sites. We acknowledge the Liverpool Clinical Trials Centre for co-ordination of the study and The Christie NHS Foundation Trust as the trial sponsor. Finally, we thank our patients and their families for taking part in this research.

References

[1] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646–674. https://doi.org/10.1016/j.cell.2011.02.013.

[2] Krzyszczyk P, Acevedo A, Davidoff EJ, Timmins LM, Marrero-Berrios I, Patel M, *et al*. The growing role of precision and personalized medicine for cancer treatment. *Technology* 2018;6:79–100. https://doi.org/10.1142/S2339547818300020.

[3] Hamburg MA, Collins FS. The path to personalized medicine. *N Engl J Med* 2010;363:301–304. https://doi.org/10.1056/NEJMp1006304.

[4] Shaw AT, Ou S-HI, Bang Y-J, Camidge DR, Solomon BJ, Salgia R, *et al*. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med* 2014;371:1963–1971. https://doi.org/10.1056/NEJMOA1406766.

[5] Drilon A, Siena S, Dziadziuszko R, Barlesi F, Krebs MG, Shaw AT, *et al*. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1–2 trials. *Lancet Oncol* 2020;21:261–270. https://doi.org/10.1016/S1470-2045(19)30690-4.

[6] Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, *et al*. Sotorasib for lung cancers with KRAS p.G12C mutation. *N Engl J Med* 2021;384:2371–2381. https://doi.org/10.1056/NEJMoa2103695.

[7] Tsimberidou AM, Iskander NG, Hong DS, Wheler JJ, Falchook GS, Fu S, *et al*. Personalized medicine in a phase I clinical trials program: the MD Anderson Cancer Center initiative. *Clin Cancer Res* 2012;18:6373–6383. https://doi.org/10.1158/1078-0432.CCR-12-1627.

[8] Massard C, Michiels S, Ferté C, Le Deley MC, Lacroix L, Hollebecque A, *et al*. High-throughput genomics and clinical outcome in hard-to-treat advanced cancers: results of the MOSCATO 01 trial. *Cancer Discov* 2017;7:586–595. https://doi.org/10.1158/2159-8290.CD-16-1396.

[9] Tsimberidou A-M, Hong DS, Ye Y, Cartwright C, Wheler JJ, Falchook GS, *et al*. Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT): an MD Anderson precision medicine study. *JCO Precis Oncol* 2017:1–18. https://doi.org/10.1200/PO.17.00002.

[10] Kim ST, Lee J, Hong M, Park K, Park JO, Ahn TJ, *et al*. The NEXT-1 (Next generation pErsonalized tX with mulTi-omics and preclinical model) trial: prospective molecular screening trial of metastatic solid cancer patients, a feasibility analysis. *Oncotarget* 2015;6:33358–33368. https://doi.org/10.18632/oncotarget.5188.

[11] Le Tourneau C, Delord J-P, Gonçalves A, Gavoille C, Dubot C, Isambert N, *et al*. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol* 2015;16:1324–1334. https://doi.org/10.1016/S1470-2045(15)00188-6.

[12] Stockley TL, Oza AM, Berman HK, Leighl NB, Knox JJ, Shepherd FA, *et al*. Molecular profiling of advanced solid tumors and patient outcomes with genotype-matched clinical trials: the Princess Margaret IMPACT/COMPACT trial. *Genome Med* 2016;8:109. https://doi.org/10.1186/s13073-016-0364-2.

[13] Flaherty KT, Gray RJ, Chen AP, Li S, McShane LM, Patton D, *et al*. Molecular landscape and actionable alterations in a genomically guided cancer clinical trial: National Cancer Institute molecular analysis for therapy choice (NCI-MATCH). *J Clin Oncol* 2020;38:3883–3894. https://doi.org/10.1200/JCO.19.03010.

[14] Rodon J, Soria JC, Berger R, Miller WH, Rubin E, Kugel A, *et al*. Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial. *Nat Med* 2019;25:751–758. https://doi.org/10.1038/s41591-019-0424-4.

[15] Camidge DR, Dziadziuszko R, Peters S, Mok T, Noe J, Nowicka M, *et al*. Updated efficacy and safety data and impact of the EML4-ALK fusion variant on the efficacy of alectinib in untreated ALK-positive advanced non-small cell lung cancer

in the global phase III ALEX study. *J Thorac Oncol* 2019;14: 1233–1243. https://doi.org/10.1016/J.JTHO.2019.03.007.

[16] Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, *et al*. Osimertinib or platinum–pemetrexed in *EGFR* T790M-positive lung cancer. *N Engl J Med* 2017;376: 629–640. https://doi.org/10.1056/NEJMoa1612674.

[17] Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol* 2018;15: 731–747. https://doi.org/10.1038/s41571-018-0113-0.

[18] Krebs MG, Blay J-Y, Le Tourneau C, Hong D, Veronese L, Antoniou M, *et al*. Intrapatient comparisons of efficacy in a single-arm trial of entrectinib in tumour-agnostic indications. *ESMO Open* 2021;6:100072. https://doi.org/10.1016/j.esmoop.2021.100072.

[19] Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, *et al*. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med* 2018; 378:731–739. https://doi.org/10.1056/nejmoa1714448.

[20] Ignatiadis M, Sledge GW, Jeffrey SS. Liquid biopsy enters the clinic — implementation issues and future challenges. *Nat Rev Clin Oncol* 2021;18:297–312. https://doi.org/10.1038/s41571-020-00457-x.

[21] McGranahan N, Swanton C. Clonal heterogeneity and tumor evolution: past, present, and the future. *Cell* 2017;168: 613–628. https://doi.org/10.1016/J.CELL.2017.01.018.

[22] Rothwell DG, Ayub M, Cook N, Thistlethwaite F, Carter L, Dean E, *et al*. Utility of ctDNA to support patient selection for early phase clinical trials: the TARGET study. *Nat Med* 2019; 25:738–743. https://doi.org/10.1038/s41591-019-0380-z.

[23] Razavi P, Li BT, Brown DN, Jung B, Hubbell E, Shen R, *et al*. High-intensity sequencing reveals the sources of plasma circulating cell-free DNA variants. *Nat Med* 2019;25: 1928–1937. https://doi.org/10.1038/s41591-019-0652-7.

[24] Bachet JB, Bouché O, Taieb J, Dubreuil O, Garcia ML, Meurisse A, *et al*. RAS mutation analysis in circulating tumor DNA from patients with metastatic colorectal cancer: the AGEO RASANC prospective multicenter study. *Ann Oncol* 2018;29:1211–1219. https://doi.org/10.1093/ANNONC/MDY061.

[25] Leighl NB, Page RD, Raymond VM, Daniel DB, Divers SG, Reckamp KL, *et al*. Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. *Clin Cancer Res* 2019;25:4691–4700. https://doi.org/10.1158/1078-0432.CCR-19-0624.

[26] Bettegowda C, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, *et al*. Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci Transl Med* 2014;6. https://doi.org/10.1126/scitranslmed.3007094.

[27] Serrano C, Vivancos A, López-Pousa A, Matito J, Mancuso FM, Valverde C, *et al*. Clinical value of next generation sequencing of plasma cell-free DNA in gastrointestinal stromal tumors. *BMC Cancer* 2020;20:99. https://doi.org/10.1186/s12885-020-6597-x.

[28] FoundationOne ® Liquid CDx. Available at: https://info.foundationmedicine.com/hubfs/FMI Labels/FoundationOne_Liquid_CDx_Label_Technical_Info.pdf . Accessed 3 May 2022.

[29] Stevenson J, Ayub M, Dransfield S, Shing E, Barley D, Dunne R, *et al*. PO-047 Etarget: a digital science solution to integrate clinical and genomic data for the manchester molecular tumour board (MTB). *ESMO Open* 2018;3:A245–A246. https://doi.org/10.1136/esmoopen-2018-EACR25.580.

[30] NHS England National Genomic Test Directory. Available at: https://www.england.nhs.uk/publication/national-genomic-test-directories/. [Accessed 17 February 2022].

Please cite this article as: Ortega-Franco A et al., TARGET National: A UK-wide Liquid-based Molecular Profiling Programme, Clinical Oncology, https://doi.org/10.1016/j.clon.2022.10.005