the first direct evidence that the Milky Way once hosted a population of extremely metal-poor globular clusters. How numerous were those clusters? The discovery of more such remnants would herald a new and exciting way of reconstructing the demographics of the lowest-mass galaxy population that contributed to the assembly of the Milky Way.

By estimating the initial masses of such extremely metal-poor globular clusters, future studies could potentially determine what fraction of their natal galaxy's mass these clusters constituted, thereby revealing how the lowest-mass galaxies formed and evolved in the early Universe. Direct observations of star-forming proto-galaxies in the early Universe could be made using NASA's James Webb Space Telescope, due to launch in 2021, and would independently test the results of such studies[10]. Finally, by comparing the orbital kinematics of fossil stellar streams with those of groups of globular clusters thought to have arrived in the Milky Way during the same accretion event[11], it might be possible to assign the streams to specific progenitor galaxies of the Milky Way.

Thanks to all-sky surveys that can detect stars with extremely low surface brightness and obtain exquisite stellar kinematics, there has been a surge in the discovery of fossil stellar streams[12], many of which probably represent the remnants of tidally disrupted globular clusters. Wan and colleagues' discovery makes it a priority to obtain accurate metallicities for all of these streams. Who knows how many relics like the Phoenix stream might be hiding in the Milky Way's halo. Now that the first one has been found, the hunt is on.

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1. Harris, W. E., Blakeslee, J. P. & Harris, G. L. H. *Astrophys. J.* **836**, 67 (2017).
2. Adamo, A. *et al. Space Sci. Rev.* **216**, 69 (2020).
3. Wan, Z. *et al. Nature* **583**, 768–770 (2020).
4. Krumholz, M. R., McKee, C. F. & Bland-Hawthorn, J. *Annu. Rev. Astron. Astrophys.* **57**, 227–303 (2019).
5. Maiolino, R. & Mannucci, F. *Astron. Astrophys. Rev.* **27**, 3 (2019).
6. Ma, X. *et al. Mon. Not. R. Astron. Soc.* **456**, 2140–2156 (2016).
7. Kruijssen, J. M. D. *Mon. Not. R. Astron. Soc. Lett.* **486**, L20–L25 (2019).
8. Beasley, M. A. *et al. Mon. Not. R. Astron. Soc.* **487**, 1986–1993 (2019).
9. Balbinot, E. *et al. Astrophys. J.* **820**, 58 (2016).
10. Pfeffer, J. *et al. Mon. Not. R. Astron. Soc.* **487**, 4550–4564 (2019).
11. Massari, D., Koppelman, H. H. & Helmi, A. *Astron. Astrophys.* **630**, L4 (2019).
12. Ibata, R., Malhan, K. & Martin, N. F. *Astrophys. J.* **872**, 152 (2019).

Medical research

An umbrella approach to test lung cancer therapies

Alexander Drilon & Matthew D. Hellmann

A clinical trial has tested the use of gene-sequencing results for lung cancer to match patients to targeted therapies. Some paired treatments were a good fit, but others did not succeed, for reasons that will require further exploration. **See p.807**

Genomic complexity is a hallmark of many cancers. Within this complexity, the identification of specific DNA alterations for which targeted therapeutic options are available has opened the door to a new era of genome-driven cancer treatment. Approved targeted therapies are in clinical use for a long list of cancer-related genomic alterations, on the basis of evidence that matched treatments lead to improvements in survival times and response (a decrease in tumour size). However, there is an ongoing need to find therapeutic matches for other, unvetted, genomic changes associated with cancer. On page 807, Middleton *et al.*[1] report a clinical trial undertaken using a framework termed an umbrella trial[2] to search for such treatment pairings. In this sort of trial, under the 'umbrella' of a single type of cancer investigated — lung cancer, in this case — the effectiveness of different targeted therapies is investigated in 'arms' of the trial, each corresponding to a tumour subset that harbours specific genomic alterations of interest.

Middleton and colleagues' research is part of the National Lung Matrix Trial. For this study, the authors focused on non-small cell lung cancers from 5,467 people in the United Kingdom. Cancer samples were tested for tumour-associated genomic alterations that could be assigned to one of the 22 trial arms. If an alteration was identified, people could be matched to a specific targeted therapy. Each alteration–therapy pairing was chosen on the basis of preclinical data from laboratory studies supporting the match. Data were reported from 288 patients (14% of the eligible population who were matched to a therapy), representing 19 of the 22 arms. The authors used a statistical method called Bayesian analysis to assess the clinical outcomes. This separated the trial results into two groups, depending on how successful the treatment outcomes were.

Those in the first group were successful matches. Certain paired treatments resulted in high response rates (more than 60% of the people treated had substantial tumour shrinkage) and durable progression-free survival (no signs of tumour growth for more than 12 months). For example, the drug osimertinib, which inhibits the receptor protein EGFR, successfully treated lung cancers associated with an alteration of a threonine to a methionine amino-acid residue (T790M) in EGFR. The drug crizotinib, which inhibits particular receptor proteins including ROS1 and MET, provided effective treatment (Fig. 1) for tumours with abnormalities in either of the genes *ROS1* or *MET*. These results are consistent with previous clinical data[3–5], which has led to the approval or recommendation of these molecularly targeted therapies in national treatment guidelines. Middleton and colleagues' results confirm the power of these mutations to predict treatment outcomes, and also highlight the transformative effect of genome-based personalized medicine in anticancer health care. The success of some personalized approaches has driven the increased adoption of DNA sequencing to identify genomic changes that then direct precision treatments in routine practice.

By comparison, outcomes were less successful in the second group. Response rates of less than 10% and short progression-free survival times were observed for most types of the paired treatments tested. Several testing arms were abandoned because they were ineffective. In cancers with mutations associated with alterations in the progression of the cell cycle, treatment with a drug that inhibits the key cell-cycle enzymes CDK4 and CDK6 achieved only a 1% response rate. The response rate was 3% in cancers with alterations in the PI3K signalling pathway that were treated with inhibitors of the proteins mTOR or AKT, which act in this pathway. A low response rate, of 7%, was found in cancers with alterations in another signalling pathway, the RAS pathway, that were treated with inhibitors of proteins that are activated by RAS (MEK, mTOR or CDK4/6).

The highest response rate in this second

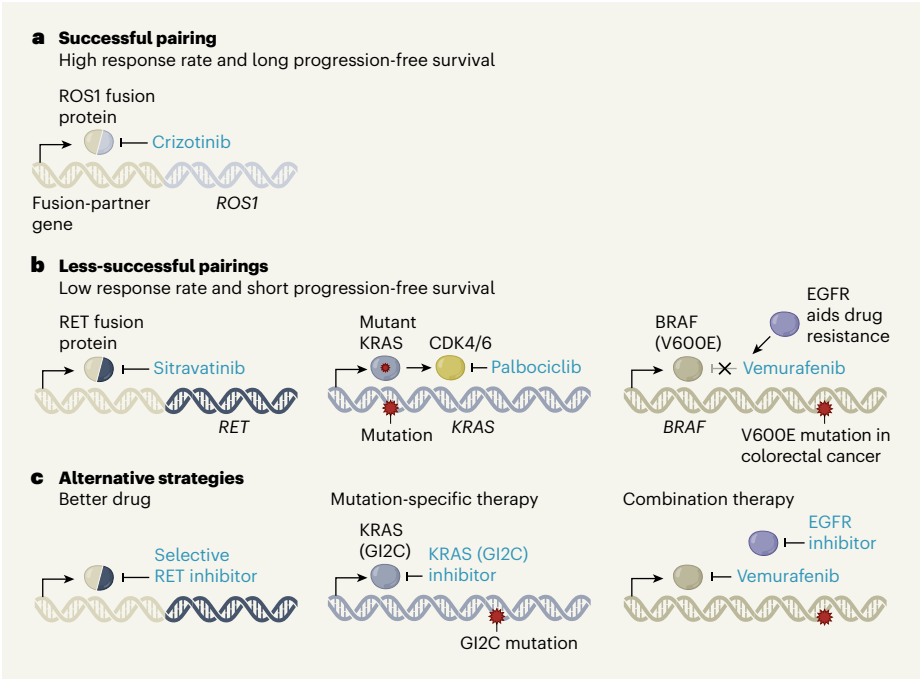

Figure 1 | Tailored cancer treatment. Middleton *et al.*[1] report the results of a clinical trial involving people with lung cancer. If individuals had DNA alterations for which laboratory evidence indicated there is an effective drug therapy, they received a matching treatment. **a**, Some pairings were successful. For example, the drug crizotinib effectively treated people whose *ROS1* gene had fused with another gene. Their tumours shrank and they had long-term progression-free survival. **b**, However, most pairings were less successful. Ineffective pairings included the use of the drug sitravatinib in individuals whose *RET* gene had fused with another gene, or treatment with palbociclib to inhibit the abnormal activation of CDK4 and CDK6 proteins that arises in people who have a mutant version of the KRAS protein. Some pairings might have failed because another protein aided drug resistance. For example, in colorectal cancer, the protein EGFR is known to prevent the drug vemurafenib from effectively targeting a BRAF protein that has a V600E mutation[6]. **c**, To target tumours that had less-successful pairings, switching to other strategies, such as the examples shown, can offer a way forward.

group was 31% (well below the response rates of at least 60% in the first group) for cancers with loss of the gene *NF1*. The loss of this gene results in MEK activation, and these tumours were treated with MEK inhibitors. However, this treatment was combined with chemotherapy, which confounded efforts to assess the dominant contributor to the response.

These results should be interpreted with care. The 'genome-driven care' baby should not be thrown out with the proverbial bathwater, even if this approach failed to identify a strong match for every genomic alteration tested. Ultimately, the success of each paired treatment depends on multiple factors – such as the right science to guide the approach, the right genomic alteration to identify those who are likely to respond, the right test to identify these alterations, and the right therapy – and these inputs might improve over time through gradual iterations.

The therapy available is often a rate-limiting factor. The trial originally had an arm that tested treatment matched to an alteration in the gene *RET*. This arm was abandoned when it became clear that the inhibitor selected was suboptimal relative to another drug that is now approved for the same purpose. In anticipation of this type of rapidly shifting landscape, future trial designs should allow potentially superior strategies to replace treatments chosen when the trial began. For example, a separate trial[6] found that in colorectal cancers associated with a particular change in an amino-acid residue in the protein BRAF – from valine to glutamic acid (V600E) – the use of a drug that inhibits BRAF had poor outcomes because of resistance to this treatment mediated by EGFR. The therapy was changed to a combination of BRAF and EGFR inhibitors, which resulted in improved clinical benefit compared with the BRAF inhibitor alone. This combination therapy is now approved for use in colorectal cancer in which BRAF has a V600E mutation.

Choosing the appropriate genomic alteration when making a targeting decision is an equally crucial consideration. Substantial variations can exist in the alterations found in a given mutated gene. For example, mutations in the gene *KRAS* examined in this trial are notably diverse. It is known that a particular change of the amino acid glycine to cysteine (G12C) in the KRAS protein offers a drug target that can be treated with G12C-selective inhibitors of KRAS. These agents have already achieved unprecedented clinical activity[7] against these formerly 'undruggable' alterations.

Other designs to optimize the efficiency of a trial can be considered. An umbrella trial limits the evaluation of the treatment to a single type of tumour. By contrast, in what are termed basket trials, participants receive a therapy regardless of their type of cancer, as long as the cancer has the genomic alteration of interest[2]. The earliest basket trials were limited to a single alteration–therapy pair. But in newer trial designs, diverse treatment options are offered to match the variety of alterations detected during DNA analysis, enabling more people to participate.

The National Lung Matrix Trial is an impressive endeavour. It demonstrates well the feasibility of comprehensive cancer-genome sequencing and the administration of several molecularly directed therapeutic interventions in one trial. It also showcases the ability of such programmes to successfully deliver anticancer health care as part of a system in which many different stakeholder groups are involved: patients, patient-advocacy groups, those working on diagnostics, academic researchers and those in the pharmaceutical industry. Future trials of this kind should focus on measures such as earlier testing and initiation of treatment, which might increase the proportion of eligible people who get treatment. The National Lung Matrix Trial was not designed to obtain official drug approvals. A trial designed with drug approval in mind would maximize stakeholder efforts, particularly if it were scaled up to involve multiple countries.

How should we move genome-driven anticancer health care forward in this decade? The protocols of the future should mimic the agile attributes of the cancers we are trying to treat. Adaptation and evolution of the various approaches in order to achieve highly flexible, global and regulatory-focused trial platforms will allow clinical science to remain both nimble and relevant amid constantly shifting sands.

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1. Middleton, G. *et al. Nature* **583**, 807–812 (2020).
2. Woodcock, J. & LaVange, L. M. *N. Engl. J. Med.* **377**, 62–70 (2017).
3. Mok, T. S. *et al. N. Engl. J. Med.* **376**, 629–640 (2017).
4. Shaw, A. T. *et al. N. Engl. J. Med.* **371**, 1963–1971 (2014).
5. Drilon, A. *et al. Nature Med.* **26**, 47–51 (2020).
6. Hyman, D. M. *et al. N. Engl. J. Med.* **373**, 726–736 (2015).
7. Govindan, R. *et al. J. Thorac. Oncol.* **14**, S208 (2019).

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