Cancer Trial Impact

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Original Article

Cancer Trial Impact: Understanding Implementation of the Short Course Oncology Treatment Trial Findings at a National Level

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Abstract

Aims: The Short Course Oncology Treatment (SCOT) trial indicated that 3 months of adjuvant doublet chemotherapy was non-inferior to 6 months of treatment for patients with colorectal cancer, with considerably less toxicity. The SCOT trial results were disseminated in June 2017. The aim of this study was to understand if SCOT trial findings were implemented in Scotland.

Materials and methods: A retrospective analysis was carried out on a dataset derived from a source population of 5.4 million people. Eligible patients were those with stage II or III colorectal cancer who received adjuvant chemotherapy. Logistic regression was applied to understand the extent of practice change to a 3-month adjuvant chemotherapy duration after the SCOT trial results were disseminated. Interrupted time series analysis was used to visualise differences in prescribing trends before and after June 2017 for the overall cohort, and by SCOT trial eligibility.

Results: In total, 2310 patients were included in the study; 1957 and 353 treated pre- and post-June 2017, respectively. The median treatment duration decreased from 21 weeks (interquartile range 14–24) prior to June 2017 to 12 weeks (interquartile range 12–21 weeks) after June 2017 ($P < 0.001$). The proportion of patients receiving over 3 months of adjuvant treatment decreased from 75% to 42% ($P < 0.001$). This change was most noticeable for patients who met the SCOT trial eligibility criteria, and specifically for those with low-risk stage III disease and those treated with capecitabine and oxaliplatin (CAPOX). Although practice change occurred in all locations, there were differences between regions that could be explained by pre-SCOT trial prescribing trends.

Discussion: A significant change in chemotherapy prescribing occurred after dissemination of the SCOT trial results. National, real-world data can be used to capture the extent of implementation of clinical trial results. In this case, implementation was aligned with clinical trial subgroup findings. This type of analysis could be conducted to evaluate the impact of other clinical trials.

Key words: Chemotherapy; clinical trial; colorectal; impact; neoplasm

Introduction

The Short Course Oncology Treatment (SCOT) trial showed that 3 months of doublet chemotherapy for patients with high-risk stage II and III colorectal cancer (CRC) was non-inferior and less toxic than 6 months of treatment [1]. The SCOT trial was a UK-led, international trial and was also the largest contributor to the International Duration Evaluation of Adjuvant chemotherapy (IDEA) collaboration that pooled data from six clinical trials, all assessing the use of shorter adjuvant doublet chemotherapy [2,3]. Although the collaboration results did not meet the pre-specified non-inferiority end point, the clinical difference between 3 versus 6 months of treatment was minimal.

Given that over 1.5 million individuals are diagnosed with CRC globally each year, and that over half present with stage II or III disease [4], these trial findings are relevant to a large group of patients. We knew, even before these trials

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were published, there was heterogeneity in prescribing practices for patients with CRC [5,6]. International survey results have indicated that these clinical trials have changed clinician attitudes to prescribing in the adjuvant setting, and have done so relatively soon after the dissemination of trial findings [7–10]. It is not yet clear if, or how, the change in clinician opinion has affected real-world practice.

The aim of this study was to examine the impact of these new research findings on clinical practice at a national level. We focused on Scotland and the impact of the SCOT trial in particular. We hypothesised that practice change would occur rapidly given that it involved a reduction in treatment and that practice change may occur to a greater extent for those patients who met the SCOT trial eligibility criteria.

Materials and Methods

This was a retrospective cohort study using routinely collected chemotherapy prescribing data linked with cancer registry and cancer audit data. Further information on acquiring these data is provided in a separate publication [11] and a list of the datasets used are detailed in Supplementary File 1.

This project was approved under the favourable ethics opinion of the East of Scotland NHS Research Ethics Service for the secondary analysis of Public Health Scotland (PHS) data within the National Safe Haven (NSH) for UK-based researchers and also had ethical approval via the broader CORECT-R initiative (CORECT-R Ethical Approval Reference: South West Central Bristol Research Ethics Committee 18/SW/0134 PBPP project number [main application]: 1718-0026 PBPP project number [PhD project]: 1718-0263).

Patient Cohort

Eligible patients were those diagnosed with stage II or III CRC between 2013 and 2018 and who underwent major surgery to remove their primary cancer, followed by adjuvant chemotherapy. Stage III disease was categorised into low (T1-3N1) or high risk (either T4 or N2), in line with extended disease stage identified in a post-hoc analysis of the SCOT trial [1] and IDEA [2]. The algorithm used to identify the cohort is described in Supplementary File 2.

Intervention

The SCOT trial results were disseminated for the first time at the American Society of Clinical Oncology (ASCO) conference in June 2017. For this analysis, patients were divided into those who commenced adjuvant chemotherapy before the results were disseminated versus those who started treatment on or after June 2017.

Statistical Analysis

Descriptive statistics

Descriptive statistics were used to analyse patient demographics and the treatments received. The median treatment duration and the proportion of patients receiving over 3 months of treatment (both calculated using the number of cycles of chemotherapy delivered rather than calendar time) were compared for pre-SCOT versus post-SCOT periods using a Mann–Whitney U and chi-squared test, respectively. It was assumed that, for any patient receiving over 3 months of chemotherapy after the SCOT results were disseminated, the intention of the treating clinician was not to change practice to align with the experimental arm of the SCOT trial. It was also assumed that the proportion of patients stopping treatment prior to 3 months due to toxicity would not change in the pre-SCOT versus post-SCOT period.

Regression using individual patient-level data

In order to investigate the impact of the SCOT trial on clinical practice while accounting for the influence of patient and disease characteristics, univariable and multivariable logistic regression was used. The characteristics included gender, age group (70 years and under versus over 70 years), Scottish Index of Multiple Deprivation (SIMD) [12], disease risk stage (stage II, low-risk stage III or high-risk stage III), treatment regimen (capecitabine and oxaliplatin [CAPOX]/raltitrexed and oxaliplatin [RALOX], 5-fluorouracil and oxaliplatin [FOLFOX], capecitabine monotherapy or 5-fluorouracil monotherapy), geographical location (South-East, West and North of Scotland), Charlson co-morbidity score (Charlson score 0, 1 or >1) [13] and disease site (colon or rectum). Logistic analysis was also repeated for subgroups of patients according to important patient and disease characteristics.

Time series analysis

In order to better visualise any change in practice around the timing of the dissemination of the SCOT trial results, data were aggregated to calculate the monthly proportion of patients receiving over 3 months of treatment. Any months containing data for fewer than five patients were excluded. The time series was analysed using a linear regression model, interrupted at June 2017, to signify the first dissemination of the SCOT trial findings.

The regression output was displayed graphically by plotting the monthly proportion of patients receiving over 3 months of treatment, alongside a regression trend line. The counterfactual situation, in which the pre-June 2017 prescribing trend continued, was also plotted. Seasonality in the time series model was checked using visual inspection of the time series plot and checks for autocorrelation were carried out by looking at residual plots and performing the Durbin–Watson test [14]. This analysis was repeated separately for patients who would have met the main SCOT trial eligibility criteria and those who would not have met those criteria.

Results

Between January 2013 and January 2018 (4.5 years before and 0.5 years after the dissemination of the SCOT trial results), 7958 patients in Scotland were diagnosed with stage

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II/III CRC (2034 [26%] from the South-East, 3774 [47%] from the West and 2150 [27%] from the North of Scotland). The median age of patients was 71 years (interquartile range 63–79). Overall, there were 3975 patients with stage II CRC and 3983 with stage III disease. In total, 7189 (90%) of these patients underwent major CRC surgery within a year of their diagnosis (stage II $n = 3666$, stage III $n = 3523$). Of those patients diagnosed with CRC, 2611 (33%) received adjuvant chemotherapy. This represented 19% ($n = 768$) of stage II patients and 46% ($n = 1843$) of patients diagnosed with stage III CRC. The proportion of patients receiving adjuvant chemotherapy was similar across the three major Scottish regions (34% South-East [$n = 698$], 32% West [$n = 1219$] and 32% North [$n = 694$]). In total, 36% of those who had undergone major surgery (stage II: 21%/stage III: 52%) received adjuvant chemotherapy. Of those patients with stage II disease who had major surgery within a year of diagnosis, 2101 (57%) had at least one high-risk disease factor and overall 667 (87%) stage II patients who received adjuvant chemotherapy fitted into the high-risk stage II category.

The final cohort for the purposes of analysing the impact of the SCOT trial on prescribing practices consisted of 2310 patients (Supplementary Figure S1). Table 1 describes the characteristics of this cohort and compares patients treated pre- and post-June 2017. Of note, in this final cohort, the proportion of patients included from the South-East after June 2017 was less compared with pre-June 2017 because granular chemotherapy prescribing records post-SCOT trial were available for a shorter period (approximately 9 months) compared with the north and west.

Practice Change

There was a significant decrease in the duration of chemotherapy delivered ($P < 0.001$) and the proportion of patients receiving over 3 months of chemotherapy ($P < 0.001$) post-SCOT compared with pre-SCOT (Table 1). The proportions of patients receiving over 3 months of treatment pre- and post-SCOT according to patient- and disease-related characteristics are outlined in Supplementary Table S1.

Logistic Regression

In the overall cohort ($n = 2310$) there was a decrease of 76% in the odds of receiving over 3 months of treatment in the post-SCOT period compared with before the results of this trial were known (Supplementary Table S2 'SCOT' unadjusted odds ratio 0.24, 95% confidence interval 0.19–0.30, $P < 0.001$). Adjusting for other factors made minimal difference to these odds (Supplementary Table S2 'SCOT' adjusted odds ratio 0.23, 95% confidence interval 0.18–0.29).

Univariable and multivariable logistic regression analysis was repeated for patient subgroups (Supplementary Table S3). Practice change was significant regardless of disease site, gender, socioeconomic status and co-morbidity. There was a large and significant change in the proportion of patients receiving over 3 months of treatment post-SCOT for patients receiving CAPOX/RALOX, whereas no significant change was seen for patients receiving FOLFOX or capecitabine monotherapy. Practice change was also significant across all locations and both age groups, although it was less marked for patients living in the North of Scotland and for patients aged over 70 years. In both instances, this was because pre-SCOT, there was already a substantial proportion of patients being treated with 3 months or less of adjuvant chemotherapy (North of Scotland [40%], aged over 70 years [28%]). Regarding disease risk stage, on adjusted analysis, there was a significant change for patients with stage III CRC, but not for those with stage II disease.

Interrupted Time Series

Figure 1 shows the monthly proportion of patients receiving over 3 months of adjuvant chemotherapy from June 2013 to May 2018 for the whole cohort. There was a significant decrease in the proportion of patients receiving over 3 months of chemotherapy after compared with before June 2017 ($P < 0.001$). There was also a significant change in the trend in the proportion of patients receiving over 3 months of treatment over time, after June 2017 compared with before this time point ($P = 0.021$) (Table 2).

The cohort was divided into patients who would have been eligible for the SCOT trial versus those who did not meet the trial entry criteria; a comparison of the patient-, disease- and treatment-related characteristics for these two groups are provided in Supplementary Tables S4 and S5. For SCOT trial eligible patients (Supplementary Figure S2), there were a significant decrease in the proportion of patients receiving over 3 months of treatment after the SCOT trial results were disseminated, whereas no significant change was observed for SCOT trial ineligible patients (Supplementary Figure S3). The interrupted time series results for the overall cohort and by SCOT trial eligibility are outlined in Table 2.

Discussion

Our findings show that the duration of adjuvant chemotherapy delivered in a real-world setting changed significantly and rapidly within months of the dissemination of the SCOT trial findings. Both the results from the SCOT trial and their incorporation into the IDEA collaboration are likely to have been important in any contribution to this practice change. The citation of research findings in clinical practice guidelines is often used as a surrogate estimate for the impact of research on clinical practice, and a previous study has estimated that it takes on average 8 years for cancer research findings to change clinical guidelines [15]. We have shown in this study that practice change occurred more quickly. Indeed, practice change in this instance pre-dated national guideline change. We suggest that the de-escalation of treatment supported by the SCOT trial and IDEA findings (and resultant cost savings for the

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Table 1
Patient characteristics

	Pre-SCOT trial (*n* (%)) *n* = 1957 (85%)	Post-SCOT trial (*n* (%)) *n* = 353 (15%)	Total (*n* (%)) *n* = 2310 (100%)
Age (years)			
Median age (IQR)	65 (57–71)	65 (57–71)	64 (55–71)
Age groups			
70 and under	1466 (75%)	261 (74%)	1727 (75%)
Over 70	491 (25%)	92 (26%)	583 (25%)
Gender			
Male	1034 (53%)	203 (58%)	1237 (54%)
Female	923 (47%)	150 (42%)	1073 (46%)
Location			
SCAN	489 (25%)	37 (10%)	526 (23%)
WoSCAN	966 (49%)	197 (56%)	1163 (50%)
NCA	502 (26%)	119 (34%)	621 (27%)
Stage			
II	593 (30%)	88 (25%)	681 (29%)
III	1364 (70%)	265 (75%)	1629 (71%)
Risk stage			
II	593 (30%)	88 (25%)	681 (29%)
Low risk III	626 (32%)	122 (35%)	748 (32%)
High risk III	738 (38%)	143 (41%)	881 (38%)
Regimen			
CAPOX/RALOX	1023 (52%)	177 (50%)	1200 (52%)
FOLFOX	164 (8%)	54 (15%)	218 (9%)
Capecitabine	709 (36%)	110 (31%)	819 (35%)
5-fluorouracil	61 (3%)	12 (3%)	73 (3%)
Site			
Colon	1530 (78%)	276 (78%)	1806 (78%)
Rectum	427 (22%)	77 (22%)	504 (22%)
SIMD			
1 (most deprived)	343 (18%)	59 (17%)	402 (17%)
2	368 (19%)	70 (20%)	438 (29%)
3	388 (20%)	90 (25%)	478 (21%)
4	399 (20%)	64 (18%)	463 (20%)
5 (least deprived)	459 (23%)	70 (20%)	529 (23%)
Charlson score			
Mean (SD)	0.54 (SD 0.92)	0.38 (0.77)	0.1 (0.9)
Median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)
Practice change			
Median treatment duration	21 weeks (IQR 14–24)	12 weeks (IQR 12–21)	18 weeks (IQR 12–24)
Proportion of patients receiving >3 months of treatment	1477 (75%)	150 (42%)	1627 (70%)

CAPOX, capecitabine and oxaliplatin chemotherapy; FOLFOX, 5-fluorouracil and oxaliplatin chemotherapy; IQR, interquartile range; NCA, Northern Cancer Alliance; RALOX, raltitrexed and oxaliplatin chemotherapy; SCAN, South-East Scotland Cancer Network; SCOT, Short Course Oncology Treatment; SD, standard deviation; SIMD, Scottish Index of Multiple Deprivation; WoSCAN, West of Scotland Cancer Network.

healthcare systems) will have made practice change easier to implement compared with adoption of additional or new therapies, and may explain the rapidity of practice change identified. This is probably due to, in part, the lack of regulatory or payer acceptance hurdles required for implementation.

We were interested to find that only half of patients in Scotland diagnosed with stage III disease during this period received adjuvant chemotherapy, in line with recent estimates from England [6,16]. This was probably driven, in part, by the fact that elderly patients are often less likely to receive chemotherapy. Of the patients diagnosed with stage II and III CRC in our cohort, the average age was over 70 years, and in the UK over 40% of individuals diagnosed with CRC are aged 75 years and over, with the highest rates in the 85–89-year-old group [17]. Despite this, the average age of patients receiving chemotherapy in our cohort was lower (65 years), in line with the demographics of the individuals recruited to the SCOT trial [1] (median age 65 years) and the IDEA collaboration trials [2] (range from median age of 61 years in CALCB/SWOG 80702 to 67 years in HORG). The proportion of patients with stage II disease receiving adjuvant chemotherapy in our cohort was less than for stage III, but this is expected because generally only patients with stage II disease who also have high-risk features will receive adjuvant chemotherapy. Also, the absolute benefit for an individual with high-risk stage II disease from receiving adjuvant chemotherapy is modest. These results show that predicting practice change based on incidence of stage II/III CRC alone would have over-estimated impact.

When practice change did occur, this was most obvious for patients who met the SCOT trial inclusion criteria, lending weight to the assumption that trial evidence contributed to the change observed. Within the SCOT trial eligible population, practice change was particularly prominent for patients receiving CAPOX. A change in practice particularly affecting patients prescribed CAPOX aligns with the results from the pre-planned subgroup analyses from the SCOT trial and IDEA, which showed that non-inferiority was met when CAPOX was used, but not for FOLFOX.

Practice change was also highest for patients with low-risk stage III disease compared with those with stage II or high-risk stage III CRC, again in line with the strength of evidence from the SCOT trial and IDEA subgroup analyses. It is interesting to note that this distinction in application of trial results by subgroup occurred even before the full SCOT trial publication was available in April 2018. This finding raises the question of whether implementation according to subgroup characteristics is justified, given the small difference between risk stages in trial outcomes for patients treated with CAPOX. There appeared to be a greater extent of practice change for patients living in the West and South-East of Scotland compared with the North, driven by the relatively high use of 3 months or less of treatment in the north in the pre-SCOT period. This requires further investigation to understand the reason that geographical location

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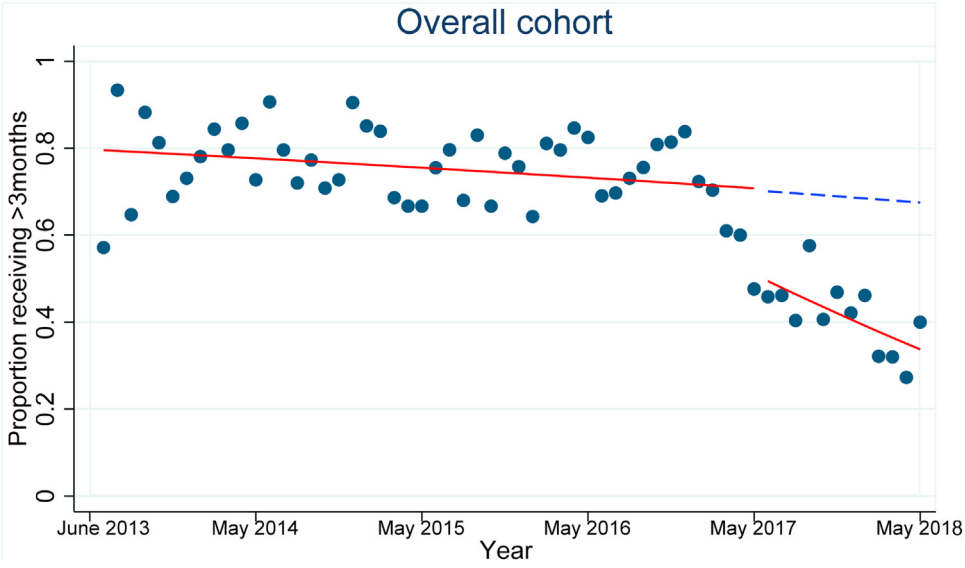

Fig 1. Change in monthly proportion of patients receiving over 3 months of treatment (overall cohort). The month signifies the date that a patient started chemotherapy. Dark blue dots: monthly proportion of patients receiving over 3 months of chemotherapy. Red line: predicted trend for monthly proportion of patients receiving over 3 months of chemotherapy using actual data. Dashed blue line: estimated trend for monthly proportion of patients receiving over 3 months of chemotherapy if the pre-SCOT trial trend continues unchanged (counterfactual). The estimated proportion of patients receiving over 3 months of treatment at the end of the study period (May 2018) was 34% (95% confidence interval 28–40%) based on actual data, compared with 67% (95% confidence interval 57–76%) based on extrapolation of the trend in the treatment duration pre-SCOT trial (absolute decrease of 33 percentage points). SCOT, Short Course Oncology Treatment.

impacted on the duration of treatment in the pre-SCOT period; reasons could include the patient case mix, including age and co-morbidity, affecting tolerability of treatment, or patient and individual clinician treatment preferences.

Overall, 17% of patients in our study had a diagnosis of rectal cancer; this compared with 18% in the SCOT trial [1]. Although we have shown a significant reduction in the proportion of patients receiving over 3 months of chemotherapy post-SCOT, the underlying assumption that an intended 6 months of treatment was an accepted standard of care pre-SCOT in this setting is less robust, and any interpretation of practice or practice change associated with implementation of trial findings must be interpreted in this context.

Few studies have investigated granular chemotherapy prescribing patterns at a national level and it is widely recognised that accessing and linking chemotherapy data to other administrative datasets can be challenging [18]. We have shown that administrative healthcare data can provide important insights into real-world treatment choices and allow analysis of if, how and when clinical trial evidence is implemented into practice, widening the generalisability of our results compared with if a local or regional-level study of prescribing practices was carried out. There is currently no standard method to monitor the uptake of new treatment strategies into practice; a further strength of this study is that we have shown how this type of analysis can be carried out.

Table 2
Interrupted time series linear regression outputs for overall cohort of patients, the Short Course Oncology Treatment (SCOT) trial eligible cohort and the SCOT trial ineligible cohort

	Overall cohort	SCOT trial eligible	SCOT trial ineligible
β_0 (intercept)	0.799 (0.732; 0.865) $P < 0.001$	0.800 (0.714; 0.886) $P < 0.001$	0.791 (0.706; 0.876) $P < 0.001$
β_1 (pre-SCOT trial time trend)	−0.002 (−0.004; 0.001) $P = 0.132$	−0.001 (−0.004; 0.002) $P = -0.625$	−0.003 (−0.006; 0.001) $P = 0.050$
Post-SCOT trial time trend (β_1 when analysis restricted to patients treated post-SCOT trial only)	−0.014 (−0.026; −0.002) $P = 0.024$	−0.016 (−0.033; 0.001) $P = 0.063$	−0.005 (−0.032; 0.021) $P = 0.650$
β_2 (level change at June 2017)	−0.215 (−0.306; −0.124) $P < 0.001$	−0.373 (−0.489; −0.256) $P < 0.001$	−0.027 (−0.203; 0.149) $P = 0.761$
β_3 (change in time trend)	−0.012 (−0.023; −0.002) $P = 0.021$	−0.015 (−0.029; 0.001) $P = 0.040$	−0.002 (−0.024; 0.019) $P = 0.829$

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One limitation of this research was that we did not have sufficient follow-up post-SCOT to compare health outcomes such as survival pre-versus post-June 2017. Second, data for patients in the South-East of Scotland were available for a shorter time period compared with data for patients in the North and West, meaning that this location was under-represented for the post-SCOT trial period. Unless the proportion of patients receiving over 3 months of treatment changed specifically for the final months of the study period in the South-East of Scotland, this probably had a limited impact on results. Finally, routine collection of patient-reported outcomes currently does not exist nationally in Scotland for CRC patients to allow evaluation of the potential decrease in toxicity or improvements in quality of life that may accompany practice change. Although we investigated patient and disease characteristics that may have influenced the extent of practice change, there may be other factors not captured by our data that were preventing practice change, contributing to unmeasured confounding.

Future research questions to be addressed include a more detailed exploration of adjuvant practice change for patients with rectal cancer, as well as investigation into health outcomes, such as survival and peripheral neuropathy, pre-versus post-SCOT. We would be interested to know if the effects of disease stage and regimen on practice are still present in the years following 2018, now that high-risk stage II results [3] and updated overall survival [19] results have been published. In addition, the reasons for the relatively low use of adjuvant chemotherapy for stage III patients in Scotland require further investigation to understand if a lower use of chemotherapy in older patients is driving that result, and more work is needed to understand why there may have been differences in practice change based on geographical location.

Conclusion

The duration of adjuvant CRC treatment reduced substantially in Scotland after June 2017, suggesting a rapid translation of trial evidence into practice. This will lead to important health and health service impact at a national level. This study has shown that national, real-world data can be used to explore and evidence implementation of clinical trial results. This type of analysis could be conducted to evaluate the impact of other clinical trials.

Conflicts of interest

C.R. Hanna reports that financial support was provided by Cancer Research UK.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2022.03.012.

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