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Somatic cancer genetics in the UK: real-world data from phase I of the Cancer Research UK Stratified Medicine Programme

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ABSTRACT

Introduction Phase I of the Cancer Research UK Stratified Medicine Programme (SMP1) was designed to roll out molecular pathology testing nationwide at the point of cancer diagnosis, as well as facilitate an infrastructure where surplus cancer tissue could be used for research. It offered a non-trial setting to examine common UK cancer genetics in a real-world context.

Methods A total of 26 sites in England, Wales and Scotland, recruited samples from 7814 patients for genetic examination between 2011 and 2013. Tumour types involved were breast, colorectal, lung, prostate, ovarian cancer and malignant melanoma. Centralised molecular testing of surplus material from resections or biopsies of primary/metastatic tissue was performed, with samples examined for 3–5 genetic alterations deemed to be of key interest in site-specific cancers by the National Cancer Research Institute Clinical Study groups.

Results 10 754 patients (98% of those approached) consented to participate, from which 7814 tumour samples were genetically analysed. In total, 53% had at least one genetic aberration detected. From 1885 patients with lung cancer, KRAS mutation was noted to be highly prevalent in UK lung adenocarcinoma at 37%. In breast cancer, rates of TP53 mutation were nearly 10-fold higher in ductal versus lobular disease. How might this impact on clinical practice?

Key questions

What is already known about this subject?

The core genetics of the six cancers explored in this article are well delineated in projects such as The Cancer Genome Atlas.

What does this study add?

- Rather than being confined to one centre/city, this study looked at very high sample numbers (eg, 1885 patients for lung cancer) across eight cities, offering a ‘snapshot’ of real-world somatic cancer genetics in the UK.
- By taking a reductionist rather than bioinformatic approach to genetic examination/analysis, we discovered a number of striking results to validate.
- For example, the KRAS mutation rate was unexpectedly high in UK lung adenocarcinoma at 37%.
- In breast cancer, rates of TP53 mutation were nearly 10-fold higher in ductal versus lobular disease.
- The core genetics of rarer pathologies such as mucinous colorectal and tubular breast adenocarcinomas were also delineated.

What is new in this study?

- This article provides an updated repository for advancing preclinical, translational and clinical cancer research.
- Establishing the prevalence of core cancer genetic aberrations provides a platform to drive forward precision medicine and molecularly targeted clinical trials.
- We also convey the challenges of setting up a nationwide infrastructure for molecular testing—an experience that we hope will be informative for other countries.
INTRODUCTION

The breadth of clinical and biological genomic challenges which have become apparent in cancer over the past five years highlights how technological advance is driving expectation ever higher. Knowledge of therapeutically targetable driver mutations in genes such as BRAF, EGFR and BRCA1/2 is now being supplemented by the discovery of a new generation of resistance mutations: these include aberrations found in the same gene, for example, EGFR T790M, or in genes downstream of the same cellular pathway such as MEK-mediated resistance in BRAF-mutated melanoma.1–4

The Cancer Research UK Stratified Medicine Programme (SMP1) was established in response to growing demand for prospective analysis of prognostic and predictive genetic markers in clinical tumour samples.5 6 At inception, there were two systemic clinical deficits in the UK National Health Service (NHS) inhibiting progress towards molecular diagnostics as a component of normal cancer care:7

1. A nationwide infrastructure facilitating key molecular pathology tests at the point of diagnosis was necessary. This would reduce waiting times involved with requesting a test in retrospect, expediting patient access to prognostic genetic information and associated genetically targeted therapies.

2. Little infrastructure existed for the systematic genomic analysis of tumour tissue surplus to diagnostic requirements, whether obtained through biopsy or resection, in the majority of patients not recruited to clinical trials.5

The central aim of SMP1 was therefore to facilitate an experience and infrastructure for molecular diagnostics in solid cancers across the UK, establishing its incorporation in the normal pathway of patient care that could be further developed during subsequent phases of the programme (SMP2). We also hypothesised that, in an era where laboratory genomic studies are offering increasing degrees of complexity, ‘bridging’ studies such as SMP1 would be necessary to ensure the ensuing data ‘storm’ runs in parallel with direct translational improvements in patient care.9 Perhaps as much progress could be gained by projects which focus on key genetic players and offer the opportunity to work backwards from identified patient responders.10–12

Here we offer a summary of important findings for implementation and clinical practice as well as core genetic results from patients across the UK in six disease areas: carcinomas of the breast, lung, colorectum, prostate, ovary and malignant melanoma.

METHODS

The Cancer Research UK Stratified Medicine Programme

The Cancer Research UK Stratified Medicine Programme (Research Ethics Committee reference 11/EE/0202) commenced in 2011, at clinical and laboratory sites in England, Wales and Scotland. Phase I (SMP1) took place between September 2011 and July 2013. Six different solid tumour types (breast, colorectal, lung, ovarian, prostate cancer and malignant melanoma) were chosen for study. Twenty-six participating hospitals formed the network, coordinated through Cancer Research UK and National Institute for Health Research-funded Experimental Cancer Medicine Centres (grouped to form local ‘Clinical Hubs’) (figure 1). At these sites, patient consent was sought for centralised molecular testing (performed at ‘Technology Hubs’) of surplus material from resections or biopsies of primary/metastatic tumour tissue, performed as part of routine clinical care.

The tumour types included in SMP1 were selected for their representation of a large percentage of the UK cancer demographic: breast, colorectal, lung and prostate cancer make up over half of all incident cancer cases in the UK each year; ovarian cancer represents the fifth most common cancer in females; advanced malignant melanoma represents a clinically unmet need which has recently been successful as a driver for a new generation of genetically targeted therapies. Also, 3–5 genes of interest were prioritised for molecular testing in each tumour type, selected by relevant National Cancer Research Institute Clinical Study Groups for their prevalence and/or potential ‘actionability’. Samples were examined for the following gene alterations: PTEN, PIK3CA, BRAF and TP53 for breast and ovarian cancer; KRAS, EGFR, ALK, BRAF and DDR2 (squamous only) for lung cancer; KRAS, NRAS, BRAF, PIK3CA and TP53 for colorectal cancer (CRC); PTEN, BRAF and TMPRSS2-ERG for prostate cancer; BRAF, NRAS, PIK3CA and KIT for melanoma. Further information on the programme and techniques
used for molecular analysis is detailed in online Supplementary methods and supplementary methods table 1.

Patient eligibility
Eligibility criteria were designed to be broad and inclusive in order to maximise the relevance of findings to the general UK population. Patients had to be aged 18 years or more, able to give written informed consent, and with a suspected or confirmed diagnosis of one of the following types of invasive malignancy: breast cancer (carcinoma including ductal, lobular and other subtypes); CRC (adenocarcinoma of the colon or rectum); lung cancer (carcinoma of the lung including both small cell and non-small cell subtypes but excluding carcinoid tumours and pleural malignant mesothelioma); malignant melanoma (advanced stage III or IV disease with at least regional lymph node involvement, from cutaneous primaries as well as less common mucosal sites); ovarian cancer (adenocarcinoma) and prostate cancer (adenocarcinoma).

Analysis, interpretation and reporting
Patients consenting to participate in the programme were required to have a sample submitted of formalin-fixed paraffin-embedded tumour tissue from a resection or biopsy procedure with surplus tissue, beyond that needed for making a tissue diagnosis, taken either from the primary tumour or from a site of metastasis.

The SMP1 gene sets for each tumour type comprised well-characterised hotspots in oncogenes, structural chromosomal rearrangements, as well as screening of multiple exons in tumour suppressor genes such as PTEN and TP53. More information on this is available in online supplementary methods.

Database analysis
For statistics, association of genotype with clinical characteristics and patient demographics were assessed using Fisher’s exact test for dichotomous factors, and the Mann-Whitney test for continuous data, which were not adjusted for multiple testing. All p values were two-sided and considered statistically significant at <0.05. More detail on database analysis, including data curation and compilation, is available in online supplementary methods.

RESULTS
Patient population
Between August 2011 and July 2013, 10754 patients (98% of those approached) consented to participate in SMP1, with 9010 patient tumour samples examined. Of 7814 samples with data available at the time of our analyses, 53% had at least one aberration detected (table 1). Also, 44% of the samples were wild type for the genes and regions analysed and the remaining 3% of samples failed all gene tests. Data completeness varied between the clinical sites and between data items (table 2).

Lung cancer
Lung cancer samples were obtained from a total of 1885 patients. The baseline demographics of these patients are shown in online supplementary table 1. In total, 774 patients (41.1%) were diagnosed with adenocarcinoma, 399 patients (21.2%) with squamous cell cancer and 50 patients (2.6%) with small cell lung cancer. Also, 64 patients (3.4%) were diagnosed with non-small cell lung cancer (NSCLC) of non-specific histological subtype (online supplementary figure 1). Due to the focus on resection samples where tissue was plentiful, the majority of samples collected represented stage I–II lung cancer (1006 samples, 53.4%), followed in frequency by stage III lung cancer (21%) then stage IV (19.4%) lung cancer. A substantial percentage of baseline information was returned as ‘not stated’ (ie, either not tested, not documented or both), the most important of which was a deficit of smoking history.

Figure 2A offers an overview of genetic results obtained from the lung adenocarcinoma population. Of those tested, 92/774 (11.9%) were EGFR mutant, 287/774 (37.1%) were KRAS mutant, 19/774 (2.5%) were ALK rearranged and 18/774 were BRAF mutant (2.3%) (online supplementary table 2). The most common failed genetic test was KRAS, with no result returned in 127/774 (16.4%) samples: incidence of gene mutation/modification would have been considerably higher, particularly for KRAS (287/647 samples, 44.36%), had these failed samples been excluded from the total numbers in our final analysis (online supplementary table 3). A further breakdown of EGFR mutation results showed that 67/92 (72.8%) EGFR-mutant cancers harboured a solitary sensitising mutation, 10/92 (10.9%) a solitary resistance mutation, 3/92 (3.3%) had both sensitising and resistance mutations and 12/92 (13%) had mutations of unknown significance (online supplementary table 4).

Table 1 Summary results of molecular analysis performed during SMP1 by tumour type

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Breast cancer</th>
<th>Colorectal cancer</th>
<th>Lung cancer</th>
<th>Malignant melanoma</th>
<th>Ovarian cancer</th>
<th>Prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of samples</td>
<td>1873</td>
<td>1605</td>
<td>1885</td>
<td>535</td>
<td>557</td>
<td>1359</td>
</tr>
<tr>
<td>Failed all tests (%)</td>
<td>5.3</td>
<td>0.9</td>
<td>2.8</td>
<td>3.6</td>
<td>3.2</td>
<td>4.0</td>
</tr>
<tr>
<td>Wild type for all genes (%)</td>
<td>45</td>
<td>19</td>
<td>64</td>
<td>31</td>
<td>40</td>
<td>52</td>
</tr>
<tr>
<td>Aberration in more than one gene (%)</td>
<td>7</td>
<td>33</td>
<td>0.5</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>
In squamous cell carcinoma, *DDR2* was mutated in 12/175 (6.9%), an incidence that becomes substantially higher if the large numbers of failed tests are excluded from analysis (12/119 samples, 10.1%). *EGFR* mutations were present in 3/399 squamous samples (0.8%), while *ALK* rearrangement was present in 2/399 (0.5%). *KRAS* (12/399 samples, 3%) and *BRAF* (5/399 samples, 1.3%) mutations were present in small numbers (online supplementary tables 2 and 3).

Forty-eight small cell lung cancers were analysed, with none of the samples harbouring a genetic mutation/modification (online supplementary tables 2 and 3).

**Breast cancer**

In total, 1873 patients with breast cancer were analysed within SMP1 (online supplementary table 5). Also, 1423 patients (76%) were diagnosed with invasive ductal carcinoma (IDC), 179 patients (9.6%) with invasive lobular carcinoma (ILC), 25 patients (1.3%) with mucinous adenocarcinoma and 55 patients (1.9%) with tubular carcinoma. Sixty-seven patients (3.6%) were diagnosed with mixed IDC/ILC (online supplementary figure 2 and table 6). Due to the focus on resection specimens, a majority of samples collected in SMP1 were taken from stage I–II breast cancer (1455 samples, 77.7%). Of patients where ER, PR and HER2 status was confirmed, ER was positive in 751/866 (86.7%) cancers, PR in 271/407 (66.6%) cancers and HER2 in 142/807 (17.6%) cancers. Only 3.2% of patients were confirmed as ‘triple-negative’ (60/1873 with ER- PR- HER2-), perhaps reflecting the relatively low percentage of stage III–IV patients recruited. Again, a substantial percentage of baseline information was returned as ‘not stated’, ranging from 35/1873 (1.8%) of patients for histological subtype to 1466/1873 (78.2%) of patients for PR status. ER and HER2 were not stated in 1007/1873 (53.8%) and 1066/1873 (56.9%) of patients, respectively.

On review of histopathological category, 420/1423 (29.5%) of IDC samples were *PIK3CA* mutant, 65/1423 (4.6%) were *PTEN* mutant, 389/1423 (27.3%) *TP53* mutant and none (0/1055 samples) were *BRAF* mutant (figure 2B and online supplementary table 6). The most common failed genetic test in IDC was *PTEN*, with no result returned in 354/1423 (24.9%) of samples tested: incidence of *PTEN* mutation would have increased to 6.1% (65/1069 samples) had these failed samples been excluded in our final analysis (online supplementary table 7). Of ILC samples, *PIK3CA* was mutated in 60/179 (33.5%), *PTEN* in 10/179 (5.6%), while *TP53* mutation was present in 6/179 samples (3.4%). Also, 25 mucinous adenocarcinomas had *PIK3CA* mutation in 3/25 samples (12%), *PTEN* mutation in 0/25 samples and *TP53* mutation in 4/25 samples (16%), while 35 tubular adenocarcinomas displayed *PIK3CA* mutation in 17/35 samples.
(48.6%), PTEN mutation in 1/35 samples (2.9%) and TP53 mutation in 0/35 samples (online supplementary table 6 and 7).

**Colorectal cancer**

CRC samples were obtained from 1605 patients (online supplementary table 8). In total, 1508 patients (94%) were diagnosed with adenocarcinoma, with mucinous adenocarcinoma representing the most common histological variant (52/1605 samples, 3.2%). Also, 579 samples (36.1%) represented TNM stage I–II CRC, 602 samples (37.5%) stage III and 241 samples (15%) stage IV. The majority of tumours were graded as moderately differentiated (1126/1605, 70.2%). Again, a substantial percentage of baseline information was returned as ‘not stated’, ranging from 17/1605 (1.1%) of patients for histological subtype to 506/1605 (31.5%) of patients for lymphovascular invasion (‘LVI’, used as surrogate marker for extramural vascular invasion in core dataset).

The vast inter-tumour heterogeneity of CRC is clearly represented despite our analysis of only five genes, including myriad double and triple combinations of genetic aberrations (figure 2C). Of adenocarcinomas tested, 581/1508 (38.5%) were KRAS mutant, 824/1508 (54.6%) were TP53 mutant, 144/1508 (9.3%) BRAF mutant, 61/1508 NRAS mutant (4%) and 158/1508 were PIK3CA mutant (10.5%) (online supplementary table 9).

The most common failed genetic test was TP53, with no result returned in 291/1508 (19.3%) of samples tested, the incidence of this mutation would have increased to 67.7% (824/1217 samples) had these failed samples been excluded from our final analysis (online supplementary table 10).

In CRC mucinous adenocarcinoma, BRAF was mutated in at least 20/52 (38.5%) of samples (online supplementary tables 9 and 10). Codon 600 BRAF V600E mutations accounted for 19 of the 20 samples from BRAF-mutated mucinous CRC. Incidence of BRAF mutation in mucinous CRC was significantly higher relative to its incidence in the SMP1 CRC adenocarcinoma population as a whole (p<0.0001). Of other genes tested, TP53 mutations were significantly less frequent (3/52 samples, 5.8%) relative to adenocarcinoma overall (p<0.0001), and PIK3CA mutations were more common (11/52 samples, 21.2%; p=0.022). NRAS and KRAS mutations were not significantly different to that observed overall.

**Prostate cancer**

Samples from 1359 patients with prostate cancer were analysed (online supplementary table 11). Adenocarcinoma histology was reported in 91.8% of cases diagnosed. In total, 430 cases (31.6%) were diagnosed at stages I–II, 238 (17.5%) were stage III samples and 78 (5.7%)
were stage IV samples. 613 (45.2%) of samples were of unknown stage.

Figure 2D offers an overview of genetic results obtained from the prostate cancer population. In adenocarcinoma samples, 11/937 (1.2%) were BRAF mutant, 67/1247 (5.4%) PTEN mutant and 501/1247 (40.2%) were TMPRSS2 rearranged. The most common failed genetic test in prostate cancer was PTEN, with no result returned in 303/1247 (24.3%) samples tested: incidence of gene mutation would have been higher, including for TMPRSS2-ERG (501/1117 samples, 44.9%), had these failed samples been excluded from our final analysis (online supplementary table 12).

**Ovarian cancer**

Ovarian cancer samples were obtained from 557 women (online supplementary table 13). In total, 360 patients (64.3%) were diagnosed with serous carcinoma, 33 patients (5.9%) with clear cell, 36 patients (6.5%) with endometrioid, 11 patients (2%) with mucinous and 72 patients (12.9%) with unspecified epithelial ovarian cancer (EOC) (online supplementary table 12 and supplementary figure 3). The most common stage at presentation was stage III ovarian cancer (268 samples, 48.1%), followed by stages I–II (117 samples, 21%), then stage IV (82 samples, 14.7%). A significant percentage of baseline information was returned as ‘not stated’, ranging from 23/535 (4.3%) of patients for gender to 438/535 (81.9%) for LVI. 232/535 patients (43.4%) were BRAF mutant, 124/535 (23.2%) NRAS mutant, 8/535 (1.5%) PIK3CA mutant and 7/535 (1.3%) KIT mutant (Figure 2F). For BRAF mutation, 219/232 samples were documented as ‘V600E’ or ‘V600E’. In total, 360 patients (online supplementary table 14). The most common failed genetic test in serous EOC was PTEN, with no result returned in 114/360 (31.7%) of samples tested: percentage mutation would have been 65.3% (181/277 samples) had these failed samples been excluded from our final analysis (online supplementary table 15).

For 33 clear cell EOCs, PIK3CA was mutated in nine samples (27.3%), PTEN mutation in four samples (12.1%), while TP53 mutation was present in seven samples (21.2%). In 36 endometrioid EOCs, PIK3CA was mutated in 9/36 samples (25%), PTEN mutation in 7/36 samples (19.4%) and TP53 mutation in 12/36 samples (33.3%). Of 11 patients with mucinous EOC, TP53 mutation was present in 5/11 mucinous samples (45.5%), with PIK3CA and PTEN mutations absent. BRAF mutation was absent in all subtypes except for serous EOC (online supplementary tables 14 and 15).

**Metastatic melanoma**

In total, 535 patients with metastatic melanoma were analysed (online supplementary table 16). A significant percentage of baseline information was returned as ‘not stated’, ranging from 23/535 (4.3%) of patients to 238/535 (43.9%) for LVI. 232/535 patients (43.4%) were BRAF mutant, 124/535 (23.2%) NRAS mutant, 8/535 (1.5%) PIK3CA mutant and 7/535 (1.3%) KIT mutant (Figure 2F).

**DISCUSSION**

We have reported results from the first UK-wide study assessing molecular pathways of cancer within the UK NHS. We focused on six common cancers (lung cancer, breast cancer, CRC, prostate cancer, ovarian cancer and metastatic melanoma), finishing with a 98% consent rate for patient participation. To the best of our knowledge, this study has offered a number of novel results relevant to our future understanding of UK cancer genetics that may also have international relevance. It also highlights a number of challenges which will be important for streamlining national molecular programmes in the future.

One key result from SMP1 was a 98% rate of patient consent for participation across all six cancer types. This success was achieved by the stipulation of a blood sample and ‘surplus’ tissue only for eligibility, that is, tissue derived from resection or biopsy, and remaining after all necessary diagnostic tests had been performed. No additional invasive procedures were necessary, and results from clinical trials that mandate further ‘research protocol’ biopsies suggest that this percentage would have been lower had patients been asked to undergo this.

One of the challenges involved with recruitment, data collection and analysis from SMP1. We believe these data offer a unique insight, unrepresented in other genomic studies: there was no planned selection bias, large patient numbers were involved and prospective assessment of important functional mutations was implemented, demonstrating the feasibility of this programme to allow nationwide patient access to relevant novel therapies, clinical trials and other research opportunities. However, results were hypothesis-generating and should be interpreted within the context of a retrospective observational analysis requiring further clinical validation. Although selection bias may be minimised in a nationwide study such as this, the potential for unplanned bias still exists: for example, a concurrent clinical trial using SMP1 to select patients with a particular cancer genotype. Expected bias included a weighting towards specific histologies and early-stage disease, given the focus on submission of resected specimens to increase the likelihood of sufficient material
being available for analysis, and the possibility that we would be more likely to recruit patients not approached for other studies due to the concern of information overload in those already participating in other research. Significant losses of important clinical information included smoking status in lung cancer, ER/PR/HER2 status in breast cancer, tumour site in CRC and loss of distinction between low-grade and high-grade serous ovarian cancers. Since implementation of this study, the collection of detailed data on each cancer diagnosed has become more established in the UK with the widespread adoption of the Cancer Outcomes Services Dataset (COSD). It is imperative that cancer treatment centres collect the key data elements within COSD which could support studies like SMP1 in the future.

SMP1 served as the basis for inception and implementation of the current second phase, SMP2, which provides patients access to molecular pre-screening of surplus diagnostic lung cancer biopsy or cytology cell block samples to inform entry to the National Lung Matrix Trial (NLM). The NLMT directly incorporates many aspects of the SMP1 infrastructure, this time facilitating multi-arm, molecularly stratified clinical trial design for patients with advanced stage non-small cell lung cancer (NSCLC). Its key aim is to demonstrate the
feasibility of combining molecular testing with clinical trial enrolment and translational progress on a national level, with its advances reported in tandem with other pioneering Cancer Research UK translational and clinical trial programmes such as TRACERx, DARWIN and PEACE.15–17

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Contributors All coauthors have made substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data. Drafted the work or revising it critically for important intellectual content, final approval of the version published. Offered agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors and coauthors
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**Data sharing statement** CRUK retains access to unpublished data from this study. Requests can be made to interrogate this further for individual cancers assessed: breast, lung, colorectal, prostate, ovarian and melanoma.

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