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Original Research

Access and quality of biomarker testing for precision oncology in Europe

Nicola Normanno [a,*], Kathi Apostolidis [b], Audrey Wolf [c], Raed Al Dieri [d], Zandra Deans [e], Jenni Fairley [e], Jörg Maas [f], Antonio Martinez [g], Holger Moch [h], Søren Nielsen [i], Thomas Pilz [j], Etienne Rouleau [k], Simon Patton [l], Victoria Williams [l]

[a] *Istituto Nazionale Tumori "Fondazione G. Pascale" - IRCCS, Naples, Italy*
[b] *European Cancer Patient Coalition (ECPC), Brussels, Belgium*
[c] *EFPIA, Brussels, Belgium*
[d] *European Society of Pathology (ESP), Brussels, Belgium*
[e] *GenQA, NHS Lothian, Edinburgh, United Kingdom*
[f] *Deutsche Gesellschaft für Pathologie E.V. (DGP), Berlin, Germany*
[g] *Sociedad Espanola de Anatomia Patologica (SEAP), Madrid, Spain*
[h] *University Hospital and University, Zurich, Switzerland*
[i] *NordiQC, Aalborg, Denmark*
[j] *QuIP GmbH, Berlin, Germany*
[k] *Gen&Tiss, Villejuif, France*
[l] *EMQN CIC, Manchester, United Kingdom*

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Abstract ***Background:*** Predictive biomarkers are essential for selecting the best therapeutic strategy in patients with cancer. The International Quality Network for Pathology, the European Cancer Patient Coalition and the European Federation of Pharmaceuticals Industries and Associations evaluated the access to and quality of biomarker testing across Europe.
Methods: Data sources included surveys of 141 laboratory managers and 1.665 patients, and 58 in-depth interviews with laboratory managers, physicians and payers. Four access metrics (laboratory access, test availability, test reimbursement, test order rate) and three quality metrics (quality scheme participation, laboratory accreditation, test turnaround time) were applied to rank the results.
Results: The access to precision medicines is higher in countries with public national reimbursement processes in place. Lack of diagnostic laboratory infrastructure, inefficient

* *Corresponding author*: Cell Biology and Biotherapy Unit, Istituto Nazionale Tumori "Fondazione G. Pascale"-IRCCS, Via M. Semmola, 80131, Naples, Italy. Tel./Fax: +39 081-5903826.
E-mail address: nicnorm@yahoo.com, n.normanno@istitutotumori.na.it (N. Normanno).

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organization and/or insufficient public reimbursement narrow the access to single biomarker tests in many European countries. In countries with limited public reimbursement, pharma and patients' out of pocket were the primary funding sources for testing. Uptake of multi-biomarker next generation sequencing (NGS) is highly varied, ranging from 0% to >50%. Financial constraints, a lack of NGS testing capabilities and the failure to include NGS testing in the guidelines represent the main barriers to NGS implementation. The quality of biomarker testing is highest in Western and Northern Europe, with more than 90% of laboratories participating in quality assurance schemes.

Conclusions: Our data clearly indicate the need for a call to action to ensure the clinical implementation of precision medicine in Europe.

1. Introduction

Knowledge of cancer has improved vastly in the last two decades. The huge variability between cancer types and between patients with the same cancer type highlight the need for—and the promise of—tailoring cancer care to individual patient characteristics [1]. Fuelled by this knowledge, cancer treatment is increasingly shifting towards precision medicine that systematically utilises patient data to inform personalised treatment decisions [2].

Significant progress has been made in the identification of biomarkers and matched therapies in oncology, with around 55% of all oncology clinical trials in 2018 involving the use of biomarkers, compared with around 15% in 2000 (https://clinicaltrials.gov/). It has been estimated that >25% of patients with cancer may receive a treatment based on biomarker testing [3,4]. In this regard, ever increasing knowledge of biomarkers is driving the use of broader tests of hundreds of genetic variants allowing for precise treatment decisions and monitoring [5–9]. In the future, the use of comprehensive biomarker testing is expected to support a shift away from traditional 'organ-of-origin' focused treatment paradigms towards the increased use of tumour-agnostic treatments based on patients' molecular features [10].

The effective use of biomarker testing and applying high quality testing standards play a fundamental role in fulfilling the potential of precision medicine to transform patient outcomes [11]. A number of processes before and following clinical laboratory testing can affect the accuracy and reliability of test results and patient safety. This is even more critical for advanced diagnostic technologies, such as next generation sequencing (NGS) or digital pathology. External Quality Assurance (EQA) programs are the key to keep testing standards high and ensure that patients can benefit from precision medicine [12–17].

The implementation of efficient biomarker testing with novel technologies is one of the key points (Flagship 6) identified in the Europe's Beating Cancer Plan (https://ec.europa.eu/files/eu_cancer-plan_en_0). The International Quality Network for Pathology (IQN Path), the European Cancer Patient Coalition (ECPC) and the European Federation of Pharmaceutical Industries and Associations (EFPIA), together with a consortium of industry and academic partners, have conducted research across the 27 European countries (EU27) and the United Kingdom (UK) in order to analyse the current biomarker testing practices in solid tumours and identify country-specific shortcomings.

2. Materials and methods

The research included a literature review on the current status of precision medicine treatment and testing in oncology, as well as interviews with key stakeholders, and two online surveys, one targeting laboratory managers and the other patients with cancer and patient advocates. The governance of the project and the survey questions are described in the supplementary material.

2.1. Laboratory survey

The laboratory manager survey, which opened in June 2020 and closed in August 2020, was aimed at providing a view of the testing landscape across biomarker test technologies in the EU27 plus UK. Invitations to participate in the survey were sent by scientific societies and EQA providers to their members. Survey responses were submitted by 141 laboratory managers from all countries, with the exception of Bulgaria and Luxembourg (Supplementary Table 1).

Respondents were active in public and private laboratories, including large hospital laboratories/academic centres (more than 400 beds or academic centres, c.70% of respondents), small/medium hospital laboratories (not affiliated with a medical school and with fewer than 400 beds, c.15% of respondents), reference laboratories (laboratories that receive specimens from other centres)

and dedicated NGS testing centres (c.15% of respondents).

The questions covered a selection of key biomarkers (Table 1), corresponding with 37 'linked' precision medicines approved by the European Medicine Agency (EMA) at the time of the survey (Supplementary Table 2). The investigated biomarkers and matched therapies are currently indicated in several types of cancer, including cancers of the lung, breast, colon, stomach and ovary and melanoma. Multi-biomarker tests refer to the use of NGS panels, ranging from targeted 50 gene panels up to whole genome/exome sequencing.

The EU27 plus UK were divided into two groups, 10 'focus' countries and 18 'additional' countries, in order to concentrate the available resources on a group of countries representative of the different European health systems. In the 10 focus countries (Germany, Spain, France, Italy, UK, Belgium, Netherlands, Sweden, Poland and Greece), both tier 1 and tier 2 biomarkers were covered as part of the analysis, while in the additional countries only the tier 1 biomarkers were investigated (Table 1). For tier 1, innovative biomarkers (NGS hotspot and comprehensive), more recently introduced immunohistochemical biomarkers (PD-L1) and already standardised molecular markers Epidermal Growth Factor Receptor (EGFR) or more recent and complex markers (BRCA, NTRK) were selected by the Executive Committee in order to get a picture of the laboratories' ability to respond to new requests (see also supplementary material). Tier 2 biomarkers include some markers introduced long ago in molecular diagnostics (HER2, ALK, ROS1, MMR/MSI and BRAF) and liquid biopsy as an innovative biomarker.

2.2. Patient survey

The patient survey (from February 2020 to September 2020) was conducted by European Cancer Patient Coalition among patients with cancer and patient advocates through national patients' organizations belonging to its network, to characterise the patient experience along the cancer diagnostic journey. The survey included questions on the following: (i) the level and quality of patient education on biomarker testing; (ii) the degree of patient satisfaction around the testing process; (iii) the availability of public reimbursement to cover the cost of biomarker testing; (iv) the availability different biomarker test technologies and test turn-around time (TAT). Overall, 1587 survey responses from 16 European countries were submitted (Supplementary Table 3).

2.3. In-depth interviews

Survey results were supplemented by in-depth interviews with 21 laboratory managers, 27 oncologists and 10 payers/commercial experts, to develop a more detailed understanding of country performance against access and quality metrics, identify potential barriers to biomarker testing as well as discuss initiatives to achieve the vision of rapid and widespread access to biomarker testing.

2.4. Data analysis

Biomarker tests were assessed according to key access and quality metrics (Supplementary Table 4) in order to evaluate the current provision of precision medicine and biomarker testing as well as the key barriers to widespread adoption of biomarker testing.

3. Results

3.1. Access to precision medicines

The access to precision medicines in EU27 and UK was ranked based on the number of medicines reimbursed out of the available medicines (Table 2). With the exception of Germany in which drug approval and inclusion into national formulary is directly linked to EMA, in most countries the approval and commercial launch of new medicines has some delays following EMA decision. Some countries were downgraded due to

Table 1
Biomarker tests covered by the research. Tier 1 tests were covered in all countries, while Tier 2 tests were covered only in 'focus' countries.

	Tier 1 biomarker tests	Tier 2 biomarker tests
Single biomarker tests: immunohistochemistry (IHC)/Fluorescence in situ hybridisation (FISH)	PD-L1	HER2 ALK MMR/MSI
Molecular (MDx): includes Polymerase Chain Reaction (PCR) and single biomarker next generation sequencing (NGS)	BRCA EGFR NTRK	BRAF ROS1
Multi-biomarker test technologies: complex genomic signatures	NGS hotspot (up to 50 genes)/targeted panel NGS comprehensive panel (more than 50 genes)	N/A N/A
Other	N/A	Liquid biopsy (ctDNA/plasma)

Table 2
Access to precision medicines.

Rank[a]	Country	N. medicines reimbursed	N. medicines available	% reimbursed
1	Germany	35	37	95%
2	Netherlands	35[b]	36	95%
3	UK	29+5[c]	36	95%
4	Spain	31[b]	33	95%
5	Italy	30[b]	33	90%
6	Denmark	29	29	100%
7	Belgium	28	29	95%
8	Croatia	28	28	100%
9	Sweden	27	35	75%
10	France	27	34	80%
11	Bulgaria	26[d]	29	90%
12	Austria	25[e]	33	75%
13	Finland	24	34	70%
14	Ireland	24	33	75%
15	Poland	23	27	85%
16	Romania	22	27	80%
17	Slovenia	20	33	60%
18	Hungary	20	25	80%
19	Greece	19	26	75%
20	Czech Republic	19	25	75%
21	Slovakia	18	31	60%
22	Portugal	18	26	70%
23	Luxembourg	17	26	65%
24	Estonia	17	23	75%
25	Lithuania	15	24	65%
26	Latvia	10	24	40%
27	Cyprus	7	27	25%
28	Malta	7	7	100%

[a] Ranking based on the number of medicines available (approved at national level and commercially launched) and % of medicine publicly reimbursed.
[b] Downgraded as some variation in reimbursement by region/hospital reported.
[c] 5 medicines available only through the cancer drug fund (CDF).
[d] Downgraded as actual availability of these medicines may be unstable, with several reports of regular medicine shortages.
[e] Some medicines may only be reimbursed on a case-by-case basis following physician request (e.g., larotrectinib).

reported variations in reimbursement by region/hospital, medicines shortage, availability only through special funds or on a case-by-case basis. Medicines access is higher in countries with public national reimbursement processes in place. However, some limits in the availability of precision medicines were identified in the majority of European countries.

3.2. Single biomarker test access

The composite score to measure single biomarker test access was based on the average proportion of laboratories offering each single biomarker test in-house or through referral, the average proportion of tests covered by public reimbursement and the single biomarker test order rate (Supplementary Table 5). Limits to the access to single biomarker tests were identified in many European countries (Fig. 1A). In the countries with the lowest performance (i.e. Slovakia, Romania, Bulgaria), diagnostic laboratory infrastructure remains underdeveloped or not efficiently organised, providing insufficient coverage. Single biomarker test access is also impeded in Southern and Eastern Europe due to lower levels of public reimbursement for testing and variability in order rates. In countries with limited public reimbursement, pharma and patients' out of pocket were the primary funding sources for testing. Timing to adoption of new tests was >1 year in 15/28 countries (Supplementary Table 5).

3.3. Multi-biomarker test access

The multi-biomarker test access score is a function of the availability of NGS testing, the capability to perform NGS testing with hotspot, small panels (<50 genes) or comprehensive panels (>50 genes), the time

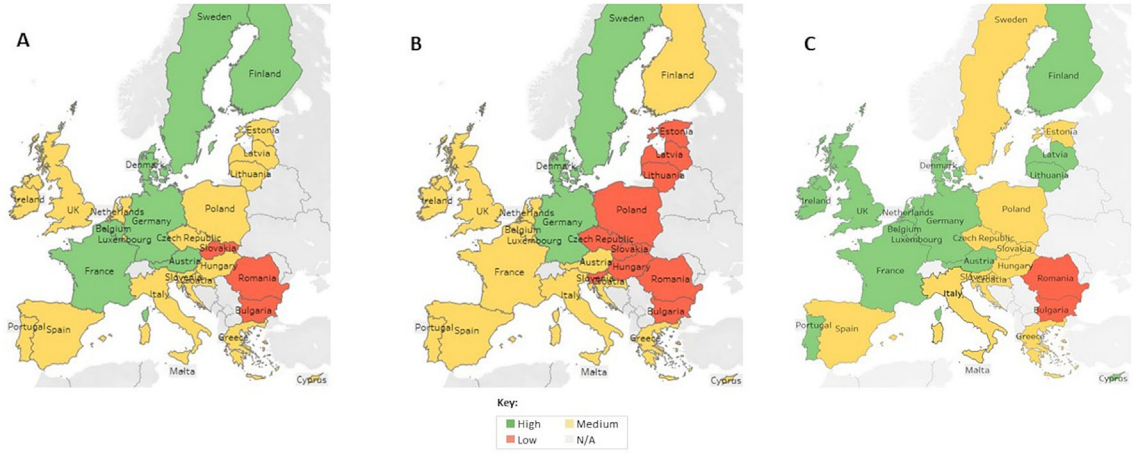

Fig. 1. The current status on quality and access to biomarker testing in Europe: (**A**) Single biomarker test access; (**B**) multi-biomarker test access; (**C**) biomarker test quality.

from introduction and the level of uptake. In addition, the average proportion of tests covered by public reimbursement and the proportion of non-small-cell lung cancer (NSCLC) biopsies tested with NGS were considered (Supplementary Table 6).

The uptake of NGS is highly varied, ranging from 0% in Slovakia to more than 50% in Denmark and the Netherlands (Fig. 1B). Low uptake can be driven by a variety of factors (Supplementary Table 6). In Eastern European countries (e.g. Slovakia, Slovenia, Bulgaria and Romania), fewer than 75% of laboratories have access to NGS technologies either internally or via referral. In Southern Europe (e.g. Spain and Greece), the use of NGS panels is limited by the availability of funding. In these countries, more than 25% of the cost of NGS testing must be covered either by the patient or by pharmaceutical sponsors. In Northern and Western European countries, the availability of NGS is generally high, with all surveyed laboratories in the UK, France, Germany, Belgium and the Nordics reporting that they have at least 1 of 3 technologies (i.e. NGS hotspot, NGS panel and NGS comprehensive panel) available in house or via referral; however, funding is often limited to certain sample types. Order rates for multi-biomarker testing for NSCLC are high (NGS testing performed in >75% of total metastatic NSCLC biopsies) in Denmark, Belgium, Cyprus, France, Sweden and Portugal. In countries with low to medium NGS order rates, key barriers include financial constraints, a lack of NGS testing capabilities and the failure to include NGS testing in the guidelines.

3.4. Biomarker test quality

The quality of biomarker testing, measured in terms of the proportion of laboratories participating in at least one EQA scheme and the extent of ISO accreditation, is highest in Western and Northern Europe, with more than 90% of laboratories participating in EQA schemes (Fig. 1C). For example, in Belgium, all molecular diagnostic laboratories must be ISO accredited for around 80% of all molecular testing procedures performed in-house and EQA participation is essential for ISO15189 accreditation [18].

In Southern and Eastern Europe, fewer laboratories report quality scheme participation (e.g. c.56% in Greece and c.78% in Italy), mainly due to a lack of dedicated funds to support participation. In some Eastern European countries, however, other factors can also play a role: for example, in Slovakia, neither EQA participation nor ISO accreditation are required for public funding or clinical trial participation.

Across Europe, TAT for single biomarker testing are generally good (mean 12.6 days; median 12 days; range 4–21 days), with only 7 countries reporting TAT >14 days (e.g. Bulgaria, Cyprus, Latvia, Poland, Romania, Slovakia and Sweden). However, longer TAT associated with multi-biomarker testing are more common, with mean TAT 17.2 days, median 15 days and range 4–40 days. In particular, 12 countries reported TAT in delivery of results >14 days (Supplementary Table 7).

3.5. Patient survey findings

Approximately 30% of the 1587 patient survey respondents reported that they had undergone biomarker testing. Testing rates were the highest for patients treated in large public hospitals, with more variable testing occurring in smaller public hospitals and in private hospitals (Supplementary Table 8).

Patients rated their satisfaction with the information received as medium in most countries except for the UK, Spain, the Netherlands and Belgium (high satisfaction) (Table 3). On average, one third of patients who underwent biomarker testing did not receive explanations by physicians during the testing process (Supplementary Table 9). However, these findings need to be interpreted with caution due to the low number of patients who responded to the survey in some countries. TAT for different stages of the biomarker testing process, from biopsy appointments to the discussion of biomarker test results with the physician, were reported to be similar

Table 3
Patient survey results: patient satisfaction with information provided by physicians[a].

Country	# of responses	Patient satisfaction with		
		Information on cancer and treatment plan	Information on testing procedure	Information on test results and implications for treatment
Belgium	16	4.6	5.4	6.4
Bulgaria	18	5.0	4.0	5.2
Croatia	50	5.2	5.3	5.7
Czech Republic	27	4.6	4.3	6.0
Denmark	26	6.5	4.5	5.2
France	16	4.3	4.3	5.4
Germany	90	5.4	5.5	5.3
Greece	163	5.4	5.3	5.4
Ireland	19	5.8	5.8	5.2
Italy	208	5.2	5.4	5.7
Lithuania	516	5.3	5.3	5.4
Netherlands	174	5.5	5.4	6.2
Poland	21	4.7	4.3	4.8
Romania	23	4.7	4.6	4.8
Spain	161	5.9	5.8	5.7
UK	59	6.1	6.3	6.2
Average	**1587**	**5.4**	**5.4**	**5.6**

[a] Respondents were asked to score their satisfaction on a scale from 1 to 7, where 1 = not satisfied at all and 7 = very satisfied 1: Has your doctor informed you sufficiently about your cancer and the planned treatment before prescribing your treatment? 2: How satisfied were you with the information you received about the testing procedure overall? 3: Were you satisfied with the breadth and depth of information given to you by your doctor about the test results and how they would/might impact your treatment?

across countries, with wait times overall longest between the time of the biopsy and the receipt of the test results (Supplementary Table 10).

4. Discussion

The increasing availability of biomarkers and matched drugs is radically changing the diagnostic and therapeutic approach to cancer. The approval of new complex biomarkers, the need to identify rare genomic alterations and the introduction of the 'tumour agnostic' biomarkers is making the use of NGS technologies increasingly indispensable for tumour genomic profiling [18,19]. The possibility for patients to access innovative therapies is directly linked to the availability of high quality biomarker tests [11].

Our research has uncovered an inconsistent picture of the access, information and quality of biomarker testing in Europe. In many European countries, there are restrictions on the availability and reimbursement of precision medicines and biomarkers tests. Surprisingly, access to tests for single biomarkers with technologies long introduced in clinical practice is also limited in several countries. In agreement with previous reports [20], we found that the lack of adequate infrastructure in some Central and Eastern European countries and more generally the presence of inadequate budgets with regional differences in reimbursement policies, make access to tests difficult for many patients. In some countries, patients must cover all or part of the cost of biomarker tests, which might contribute to the "'financial toxicity" associated with cancer [21].

In several countries, there is no link between precision medicine and matched biomarker test approval. As consequence, the price authorization and reimbursement of biomarker test delay considerably compared with the approval of the medicines. This misalignment in procedures contributes to delaying the introduction of new tests in clinical practice and represents a 'de facto' limitation to access to new drugs. This problem has been addressed and resolved in some countries. In Belgium, the so-called Platform CDx includes competences of the Commission for Reimbursement of Medicines and the Technical Medical Council, which provides advice on the practices and the tests to be reimbursed by the healthcare system [22].

In Europe, less than 10% of specimens requiring the molecular testing are currently analysed with NGS, with many countries reporting less than 2% of tumours tested. International guidelines recommend the use of NGS for biomarker testing in NSCLC [18]. We found that the fraction of NSCLC cases for which an NGS test is being performed today at diagnosis is less than 50% for many European countries. These data are similar to those reported for community hospitals in the United States [23], underlining how the problem of NSCLC sub-genotyping is unfortunately relevant across various healthcare systems. Indeed, a global survey on molecular profiling in lung cancer confirmed that less than 50% of patients receive biomarker testing [24]. In agreement with our findings, several barriers to biomarker testing were identified including cost, quality of samples, access, awareness and timing.

The quality of biomarker testing is essential to ensure appropriate treatment for patients with cancer. We found that participation in EQA schemes is not mandatory for most European countries and few laboratories have received ISO accreditation. Several studies have shown that the quality of the new tests introduced in clinical practice is often limited and only the participation in EQA schemes can detect methodological errors that can have serious consequences on patients' outcome [25].

Patients are increasingly informed and take an active part in the decision on the therapeutic strategy. An area of opportunity was identified given that one third of the patients surveyed did not receive enough information on biomarkers and biomarker tests indicated for their cancer. These data underline the need for continuous education of all stakeholders to ensure that patients are properly informed about all available therapeutic options and their implications [26].

Our data indicate the need for a call to action to ensure the clinical implementation of precision medicine in Europe. In fact, the expected increase in approved agnostic therapies will lead to an increase of the number of patients to be analysed for biomarkers and, probably, of the cases candidates for NGS tests, whose capacity is currently highly limited. In this respect, our group identified a few general recommendations to improve this system. A process should be developed for the parallel regulatory and reimbursement approval of the precision medicine and the associated biomarker test. Investments in testing infrastructure and training of test personnel are definitely required. An adequate budget must be identified to be allocated to biomarkers, to meet all needs. A stringent system for verifying the quality of the tests must be implemented to guarantee patient safety. These initiatives are urgent to remove the barriers to biomarker test access and therefore guarantee equal access to the new therapeutic possibilities for all European patients, as highlighted in the European Code of Cancer Practice (https://www.europeancancer.org/2-standard/66-european-code-of-cancer-practice) and in the Europe's Beating Cancer Plan. Furthermore, they are essential to ensure the development in Europe of precision medicine, which in the future will rely more and more on the integration of routine clinical genomic analysis with clinical data [27]. Many European countries risk being excluded from this progress if the issues identified by our survey are not addressed and resolved.

Author contributions

Study design: N. Normanno, K. Apostolidis, A. Wolf, Definition and distribution of questionnaires, data collection and analysis: N. Normanno, K. Apostolidis, A. Wolf, R. Al Dieri, Z. Deans, J. Fairley, J. Maas, A. Martinez, H. Moch, S. Nielsen, T. Pilz, E. Rouleau, S. Patton, V. Williams, Drafting of the manuscript: N. Normanno, Approval of the manuscript: N. Normanno, K. Apostolidis, A. Wolf, R. Al Dieri, Z. Deans, J. Fairley, J. Maas, A. Martinez, H. Moch, S. Nielsen, T. Pilz, E. Rouleau, S. Patton, V. Williams.

Role of the funding source

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: N. Normanno declares: speaker's fee and/or advisory boards from MSD, Bayer, Biocartis, Illumina, Incyte, Roche, BMS, MERCK, Thermofisher, Astrazeneca, Eli Lilly; financial support to research projects (institutional grants) from MERCK, Thermofisher, QIAGEN, Roche, Astrazeneca, Biocartis, Illumina; non-financial interests President of the International Quality Network for Pathology (IQN Path) and President of the Italian Cancer Society (SIC).

K. Apostolidis declares no conflicts of interest.

A. Wolf declares employment in EFPIA.

R. Al Dieri declares no conflicts of interest.

Z. Deans declares paid employment as Deputy Director, Genomics Unit, NHS England and NHS Improvement; consultancies from AstraZeneca, MSD; educational grants from AstraZeneca, MSD, Qiagen, Eli Lilly.

J. Fairley declares Advisory Board for Eli Lilly and paid lectures for AstraZeneca.

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T. Pilz declares no conflicts of interest.

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Appendix A. Supplementary data

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