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ORIGINAL RESEARCH ARTICLE

Next-Generation Sequencing in Clinical Practice: Is It a Cost-Saving Alternative to a Single-Gene Testing Approach?

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Abstract

Objectives This study aimed to compare the costs of a next-generation sequencing-based (NGS-based) panel testing strategy to those of a single-gene testing-based (SGT-based) strategy, considering different scenarios of clinical practice evolution.

Methods Three Italian hospitals were analysed, and four different testing pathways (paths 1, 2, 3, and 4) were identified: two for advanced non-small-cell lung cancer (aNSCLC) patients and two for unresectable metastatic colon-rectal cancer (mCRC) patients. For each path, we explored four scenarios considering the current clinical practice and its expected evolution. The 16 testing cases (4 scenarios × 4 paths) were then compared in terms of differential costs between the NGS-based and SGT-based approaches considering personnel, consumables, equipment, and overhead costs. Break-even and sensitivity analyses were performed. Data gathering, aimed at identifying the hospital setup, was performed through a semi-structured questionnaire administered to the professionals involved in testing activities.

Results The NGS-based strategy was found to be a cost-saving alternative to the SGT-based strategy in 15 of the 16 testing cases. The break-even threshold, the minimum number of patients required to make the NGS-based approach less costly than the SGT-based approach, varied across the testing cases depending on molecular alterations tested, techniques adopted, and specific costs. The analysis found the NGS-based approach to be less costly than the SGT-based approach in nine of the 16 testing cases at any volume of tests performed; in six cases, the NGS-based approach was found to be less costly above a threshold (and in one case, it was found to be always more expensive). Savings obtained using an NGS-based approach ranged from €30 to €1249 per patient; in the unique testing case where NGS was more costly, the additional cost per patient was €25.

Conclusions An NGS-based approach may be less costly than an SGT-based approach; also, generated savings increase with the number of patients and different molecular alterations tested.

1 Introduction and Research Question

Next-generation sequencing (NGS) is a technology that allows the simultaneous sequencing of selected regions of the genome [targeted sequencing (TS)] up to the whole exome [whole exome sequencing (WES)] or whole genome [whole genome sequencing (WGS)] [1, 2]. NGS is currently used to identify mutations for diagnostic and therapeutic purposes in clinical practice (CP) or in the context of specifically designed clinical trials [3].

Growing interest in NGS has raised the question of its value for money (cost-effectiveness) and sustainability

Key Points for Decision Makers

Testing strategies for advanced non-small-cell lung cancer and unresectable metastatic colon-rectal cancer patients can vary among Italian hospitals in terms of molecular alterations tested and testing techniques used.

Decreasing the adoption of single-gene testing (SGT) techniques in favour of next-generation sequencing (NGS) use can lead to cost reduction. Testing a minimum number of patients and molecular alterations might be necessary to generate savings.

The number of different molecular alterations to be tested is expected to grow in the near future along with the potential savings generated by the use of NGS.

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(budget impact) compared to the traditional single-gene testing (SGT) approach.

In Italy, the SGT-based approach is usually carried out in laboratories where the NGS technology is not available, and consists of detecting those biomarkers that are druggable with treatments approved and reimbursed by the Italian Drug Agency (AIFA). For example, advanced non-small-cell lung cancer (aNSCLC) patients can be treated with specific anti-epidermal growth factor receptor (anti-EGFR), anti-anaplastic lymphoma kinase (anti-ALK), or anti-receptor tyrosine kinase (anti-ROS) drugs; these biomarkers can be tested with single tests based on real-time polymerase chain reaction (RT-PCR), single-gene sequencing, in situ hybridization techniques, and immunohistochemistry. Alternatively, the NGS-based approach aims at simultaneously evaluating all the actionable biomarkers regardless of AIFA approval and reimbursement.

Three recent papers investigated the challenges posed by economic evaluations applied to NGS [4] and systematically reviewed the most recent evidence on the economic impact of the NGS-based versus SGT-based approach [5, 6]. For cost estimates, these reviews found huge variations in both methods (e.g. gross costing vs bottom-up approach) and their findings. Some studies estimated the comprehensive diagnostic pathway costs (including patient consultations and admissions), while others focused on genetic sequencing. The reviews raised criticisms not only for the heterogeneity of methods used, but also because many cost analyses did not present data transparently and did not fully declare the cost items included [5], thus limiting data comparability and transferability. Review authors advocated for the production of guidelines on the costing of diagnostic pathways [6]. The main limitations found in the studies included in the reviews are that they (1) rarely relied on microcosting, which is particularly required for testing in heterogeneous patient populations; (2) were mostly retrospective analyses, whose completeness depends on data availability; (3) represented a broad clinical spectrum of genetic disorders; (4) were often carried out on a small sample size; and (5) adopted a simplistic approach, assuming that NGS may substitute all current procedures adopted as SGT.

The present study aimed to compare the costs of the NGS-based approach with different TS panels to those of the SGT-based approach, overcoming most of the limitations raised for other studies and adopting a dynamic approach, i.e. comparing different testing scenarios, where NGS with different TS panels is gradually integrated into the SGT-based approach. Furthermore, we estimated the threshold, in terms of the number of patients, where the NGS-based approach becomes less costly than the SGT-based approach.

The analysis has been carried out in Italy, where NGS testing is currently not reimbursed at the national level, since it is not included in the Italian basket of healthcare goods and services centrally defined by the national Ministry of Health. However, the regions that are responsible for the delivery of healthcare and the relevant budget may provide health services beyond this level at their own expenses [7]. Since inpatient and outpatient services, including diagnostic testing, are paid on a fee-for-episode basis, reimbursement of NGS at the regional level would require that the Regional Government set the relevant fee. According to a report published in 2017, this has happened only in the largest Italian region (Lombardy) so far (€2072) [8]. The same report illustrates the availability of NGS sequencers in four regions, accounting for 35% of the Italian population: at least one NGS sequencer in 40% of hospitals (our elaboration on [8, 9]), with an estimate of one sequencer per 2.4 per million inhabitants. There is not, to our best knowledge, a nationwide analysis of the use of NGS technologies in Italy.

The current analysis focused on non-small-cell lung cancer (NSCLC) and unresectable metastatic colon-rectal cancer (mCRC). NSCLC is the first and third leading cause of tumour-related deaths in Italy for men (26% of deaths) and women (11% of deaths), respectively. The diagnosis frequently occurs in advanced stages (aNSCLC), where the current therapies have limited efficacy, contributing to poor outcomes (15.8% 5-year survival rate) [10]. Unresectable mCRC is the second most frequent cancer in Italy both in terms of incidence and deaths, with a 5-year survival rate of 66% (colon cancer) and 62% (rectal cancer) [10]. Both diseases can be treated with targeted therapies, but the future role played by NGS-based techniques has been differently envisaged, with an expected increasing importance for NSCLC [11, 12] and higher uncertainty for mCRC.

2 Methods

The comparison between the SGT-based and NGS-based approaches in molecular alteration testing focused on aNSCLC and mCRC patients (first- and second-line treatments), with 45% of patients treated with second-line therapy for aNSCLC [13] and 49.5% of patients treated with second-line therapy for mCRC [14]. The cost analysis was conducted considering the hospital perspective.

The molecular alterations considered were as follows:

- *aNSCLC*: epidermal growth factor receptor (*EGFR*), kirsten rat sarcoma viral oncogene (*KRAS*), mesenchymal-epithelial transition factor (*MET*) exon 14 skipping, and B-Raf and V-Raf murine sarcoma viral oncogene homolog B (*BRAF*) mutations; anaplastic lymphoma kinase (*ALK*), ROS proto-oncogene 1 receptor tyrosine kinase (*ROS-1*), and rearranged during transfection (*RET*) fusions; mesenchymal-epithelial transition factor (*MET*) amplification; human epidermal growth factor

receptor 2 (*HER2*) status (copy number alteration or mutation, protein expression); programmed death-ligand 1 (PD-L1) status; microsatellite instability (MSI); and tumour mutational burden (TMB);

- *mCRC*: *KRAS*, neuroblastoma rat sarcoma viral oncogene (*NRAS*), and *BRAF* mutations; PD-L1 status; O6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation; MutL homolog 1 (MLH1), MutS homolog 2 (MSH2), postmeiotic segregation increased 2 (PMS2), and MutS homolog 6 (MSH6) protein expression; *HER2* and *EGFR* status (copy number alteration, protein expression); MSI; *RET* and *NTRK1/NTRK2/NTRK3* pan neurotrophic tropomyosin receptor kinase (PANTRK) fusions; fibroblast growth factor receptor (*FGFR2*) gene status; and TMB.

Three Italian hospitals were selected through convenience sampling [15] based on hospital willingness to participate and expertise in the diseases considered:

- Scientific Institute for Research, Hospitalisation and Health Care (IRCCS) *Istituto Nazionale dei Tumori* (INT) (Milan), which was the pilot centre supporting the research protocol design (aNSCLC and mCRC tests accounted for 60% of the laboratory activity)
- Teaching Hospital Trust Sant'Andrea (Rome) for aNSCLC (whose tests accounted for 75% of the laboratory activity)
- IRCCS Istituto Candiolo (Turin) for mCRC (whose tests accounted for 10% of the laboratory activity).

Only one hospital was considered for both aNSCLC and mCRC; hence, four testing pathways (paths 1, 2, 3, and 4) were investigated, two for each target disease (Fig. 1).

The number of aNSCLC patients tested per year were 364 and 317 for paths 1 and 2, respectively; mCRC patients tested per year were 260 and 225 for paths 3 and 4, respectively (2016–2018 average).

Input data were collected through interviews based on a semi-structured questionnaire and administered to a CRC/NSCLC oncologist, pathologist, biologist/molecular biologist, or laboratory technician. Aggregated data were collected without tracking patient-specific information. The pilot hospital (INT) was more intensively involved, with six interviews conducted for each path. Information was organized in a data collection template, validated with follow-up interviews, and cross-validated with the interviewees through a direct check of the template. For the other hospitals, a single interview was conducted with all the involved healthcare professionals, and a similar approach to the INT review was used. Volume and cost data were collected by responders; time spent performing testing was derived from a perceptual response based on laboratory staff experience.

For each path, four scenarios were considered:

- *Clinical Practice* (CP) scenario (i.e. current testing pathway).
- "*Minimum set*" scenario, in which molecular tests were carried out if strongly recommended by the Italian oncological guidelines [16, 17]. This scenario is usually more conservative than the CP scenario.
- "*Future CP without TMB*" scenario, in which gene testing was expanded to mutations that are expected to be routinely included in the future, excluding TMB, i.e. a measurement of the mutation load carried by the tumour cells that represents a putative predictive biomarker for immune therapy [18].
- "*Future CP*" scenario, in which the CP scenario was extended to mutations that are expected to be included in future as well as TMB analysis.

The four scenarios were analysed for each of the four paths. For the resulting 16 testing cases, two alternative testing approaches were compared:

- *SGT-based* approach, where molecular alterations were tested with single-gene techniques [e.g. fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), Sanger sequencing, immunohistochemistry] and NGS was used only if standard techniques were unsuitable (e.g. for TMB testing).
- *NGS-based* approach, where molecular alterations were tested, as much as possible, through NGS panel testing; otherwise, SGT techniques were adopted.

A comparison of the NGS-based and SGT-based approaches was conducted as a variation in the transition from an SGT-based approach to an NGS-based approach (hereafter referred to as $\Delta_{SGT \rightarrow NGS}$).

The cost items considered were personnel, consumables, equipment (purchasing and maintenance), and overheads; cost data refer to the year 2018–2019.

For each technique and molecular alteration, the time spent by each healthcare professional involved in the testing activities was investigated. Given the proportion of fixed and variable time defined for each activity, the overall personnel time absorbed varied with the average machine saturation (number of samples per run). Saturation depended on the volumes of tests performed, maximum number of samples per run, laboratory opening hours, and required time for result delivery (14 calendar days) [19–21]. Considering the machine time required to perform the test and personnel reporting activities, 8 working days was assumed as the deadline to setup the machine and begin the run.

The personnel time absorbed was monetized using the hourly gross salary (€61670/year, €61601/year, and €73047/

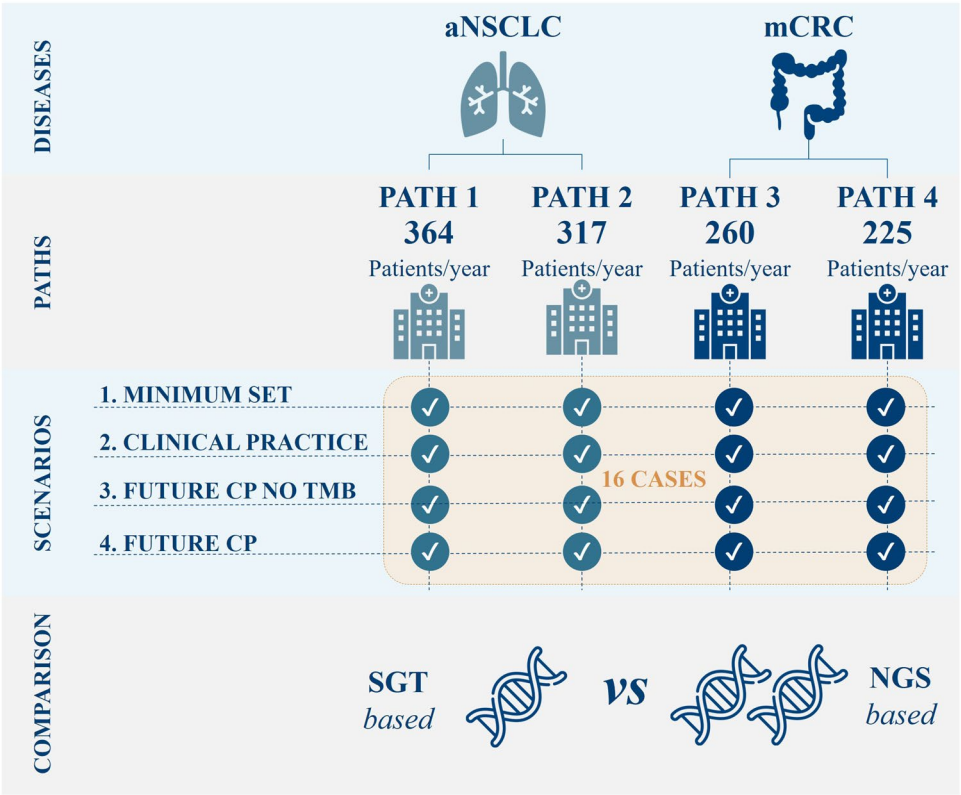

Fig. 1 Research design. Two testing pathways for each of the diseases considered (paths 1 and 2 for aNSCLC and paths 3 and 4 for mCRC) were investigated in three Italian hospitals. Four scenarios ("minimum set", "clinical practice" (CP), "future CP no TMB", and "future CP") were defined for each testing pathway, and cost analyses were conducted comparing the SGT-based and NGS-based approaches for each of the 16 testing cases identified. *aNSCLC* advanced non-small-cell lung cancer, *CP* clinical practice, *mCRC* metastatic colon-rectal cancer, *NGS* next-generation sequencing, *SGT* single-gene testing, *TMB* tumour mutational burden, *vs* versus

year for laboratory technicians, biologists, and pathologists, respectively) [22].

Consumables costs were provided for each combination of techniques and molecular alterations tested. Unit costs [including institutional discounts and value-added tax (VAT)] were obtained from purchase orders, reflecting the actual costs sustained by the hospitals. In particular, NGS consumables costs refer to the Ion Torrent™ Ion S5 System, provided by one of the involved hospitals and validated by the other two.

Equipment purchasing costs were provided by the accounting team of one of the involved hospitals. As for the consumables, NGS equipment costs refer to the Ion Torrent™ Ion S5 System. The other two hospitals did not provide their own data, but confirmed that those provided could be used as a reference in the analysis. An alternative approach was identified in the adoption of publicly available tenders for Italian hospitals (years 2017–2018),[1] but the data were too variable to be considered. Investment depreciation was set to 5 years [8], while the annual maintenance cost was assumed to be 10% [23] of the machine purchasing cost. Since aNSCLC/mCRC testing partially accounted for the total machine activity, the proportion of time dedicated to performing aNSCLC/mCRC tests for each technique was applied, and acquisition costs were re-proportionated accordingly (Annex Table 1, see the electronic supplementary material). We assigned to each scenario only those equipment and maintenance costs that refer to the specific techniques used.

The hospitals involved did not provide the overhead costs, and even if they had been provided, the different allocation approaches in use (e.g. level of data aggregation, cost items included, allocation drivers) would have made it difficult to obtain a sound comparison of the specific amount allocated to each technique. Furthermore, there is no reference in the Italian literature that can provide guidelines on overheads allocation in our specific case. Therefore, we decided to adopt the approach used by Schwarze et al., where total costs were increased by an additional 20% to account for overheads [24].

For each path, an evaluation with varying volumes of tested patients was performed to identify the minimum number of patients beyond which the NGS-based approach became less costly (break-even analysis).

Single-way deterministic sensitivity analysis (DSA) was performed for the CP scenario to identify the key model drivers. Each parameter was varied by ± 20%. Savings generated by NGS adoption increased in more advanced scenarios, thus the choice of performing the analysis in the CP scenario can be considered a conservative approach.

[1] Supplementary material on request.

3 Results

The results section reports (1) an overview of the input data (further information is reported in the annex, see the electronic supplementary material), (2) the mean cost per patient, (3) the personnel time and cost absorbed for testing activities, (4) the capacity increase, (5) the break-even analysis, and (6) the sensitivity analysis.

The results are based on the $\Delta_{SGT \rightarrow NGS}$ comparison, and a discussion is presented in the sections below. A complete illustration of the results achieved for each testing case is provided in Table 1.

3.1 Input Data

The analysis considered the following for each path:

- *Molecular alterations tested and testing frequency* upon the first and second treatment lines in each scenario (Annex Table 2, see the electronic supplementary material)
- *Testing techniques* for each molecular alteration, including NGS (Annex Table 3, see the electronic supplementary material)
- *Validation and retesting frequency for each molecular alteration* in case of failure or an inconclusive result and the type of technique adopted (Annex Table 4, see the electronic supplementary material)
- *Time required to perform testing and reporting activities* for each healthcare professional involved (Annex Table 5, see the electronic supplementary material)
- *Equipment costs* including purchase, depreciation and maintenance costs (Annex Table 1, see the electronic supplementary material)
- *Consumables costs* for each technique and molecular alteration tested (Annex Table 6, see the electronic supplementary material)
- *Overhead costs* calculated as percentage (20%) of the resulting total cost.

Participating hospitals differed in terms of molecular alterations currently tested, expected evolution of the testing approach, and techniques adopted. These differences led to a different average number of tests per patient (Table 2), ranging from one (path 4), meaning that all the alterations are tested with the NGS panel test, to nine (path 3) for the NGS-based technique, and from 1.3 (path 4) to 12.5 (path 3) for the SGT-based technique. Moving from the "minimum set" to the "future CP" scenario, the number of tests per patient increased, although to a lesser extent, using the NGS-based approach, which allows simultaneous testing. The remarkable difference between path 3 and path 4 in terms of average number of tests per patient is mainly due to the considerably wider set of molecular alterations tested in path 3 compared to path 4 (Table 2).

3.2 Mean Cost Per Patient

The mean cost per patient, including personnel, consumables, equipment, and overhead costs, is reported in Fig. 2.

The $\Delta_{SGT \rightarrow NGS}$ savings per patient increased in scenarios with a larger set of molecular alterations tested. Savings in the "minimum set" and "future CP" scenarios ranged from €288 to €879, from −€25 (the only case of a cost increment) to €522, from €63 to €633, and from €30 to €1249 for paths 1, 2, 3, and 4, respectively.

The NGS-based approach reduced personnel costs in all testing cases. The consumables $\Delta_{SGT \rightarrow NGS}$ costs were reduced in all of the testing cases except for path 2 in the "minimum set" and CP scenarios. In path 2, less expensive SGT techniques were preferred to more expensive techniques adopted by other hospitals, making the $\Delta_{SGT \rightarrow NGS}$ savings more difficult to achieve. Consumables were the most relevant cost item, and the savings achieved compensated for the potential increase in equipment costs. Equipment costs increased from the "minimum set" scenario to the "future CP" scenario since more molecular alterations need to be tested and more testing techniques need to be used. Overhead costs are proportional to the total cost of personnel, consumables, and equipment. The NGS capacity to test multiple molecular alterations caused the NGS-based approach to be less costly than the SGT-based approach in scenarios with more comprehensive testing, generating equipment cost savings in half of the testing cases considered.

The overall cost comparison is discussed in the following sections and is summarized in Table 1.

3.3 Personnel Time

$\Delta_{SGT \rightarrow NGS}$ personnel time savings increased progressively in scenarios based on more comprehensive testing.

The $\Delta_{SGT \rightarrow NGS}$ overall personnel time savings were 628 h, 271 h, 103 h, and 333 h for paths 1, 2, 3, and 4, respectively, in the "minimum set" scenario and 1369 h, 691 h, 470 h, and 919 h, respectively, in the "future CP" scenario (Fig. 3).

The overall time savings for each path are reported in Fig. 3. Personnel cost savings, as reported in Table 1, were proportional to time savings, ranging from €3618 (path 3, "minimum set") to €48,216 (path 1, "future CP").

Personnel time saved was converted into the number of additional patients who could be potentially tested by the hospital (Table 3) using an NGS-based approach, providing an estimation of the capacity increase. This indicator was calculated by dividing the overall personnel time savings

Table 1 Comparison between SGT-based and NGS-based strategy (cost and personnel time)

		aNSCLC								mCRC							
		Path 1				Path 2				Path 3				Path 4			
		Minimum set	CP	Future CP no TMB	Future CP	Minimum set	CP	Future CP no TMB	Future CP	Minimum set	CP	Future CP no TMB	Future CP	Minimum set	CP	Future CP no TMB	Future CP
Results per patient																	
Cost per patient (€/pt)	SGT-based	845	1203	1219	3420	476	592	696	2760	1018	1501	1505	3783	678	1267	1249	3561
	NGS-based	557	643	643	2541	501	562	562	2238	955	1308	1374	3150	648	648	648	2311
	$\Delta_{SGT \rightarrow NGS}$ savings	288	560	577	879	− 25	30	134	522	63	193	131	633	30	619	602	1249
Overall results																	
Personnel time (h)	SGT-based	1147	1564	1642	2360	710	807	853	1326	852	1483	1453	1931	596	955	919	1303
	NGS-based	519	619	619	991	439	497	497	635	750	1186	1251	1461	263	263	263	384
	$\Delta_{SGT \rightarrow NGS}$ savings	628	946	1023	1369	271	309	356	691	103	297	202	470	333	692	655	919
Personnel cost	SGT-based	41	55	58	83	27	30	32	49	30	53	52	69	22	35	33	47
(‘000 €)	NGS-based	18	22	22	35	16	18	18	23	27	42	45	52	9	9	9	13
	$\Delta_{SGT \rightarrow NGS}$ savings	22	33	36	48	11	12	14	25	4	11	7	17	12	26	24	33
Consumables cost (‘000 €)	SGT-based	193	29	29	91	87	103	129	641	179	244	246	662	74	123	121	480
	NGS-based	113	136	136	699	98	110	110	548	109	156	168	545	52	52	52	36
	$\Delta_{SGT \rightarrow NGS}$ savings	79	151	153	215	− 11	− 7	19	92	70	88	78	117	23	71	69	120
Equipment: purchasing and maintenance cost (‘000 €)	SGT-based	23	23	23	40	12	23	23	40	11	29	29	89	31	80	80	141
	NGS-based	37	37	37	37	18	20	20	20	71	85	85	85	60	60	60	60
	$\Delta_{SGT \rightarrow NGS}$ savings	− 14	− 14	− 14	3	− 6	3	3	20	− 60	− 57	− 57	4	− 29	20	20	80

Table 1 (continued)

		aNSCLC								mCRC							
		Path 1				Path 2				Path 3				Path 4			
		Minimum set	CP	Future CP no TMB	Future CP	Minimum set	CP	Future CP no TMB	Future CP	Minimum set	CP	Future CP no TMB	Future CP	Minimum set	CP	Future CP no TMB	Future CP
Total cost ('000 €)	SGT-based	256	365	370	1037	126	156	184	729	221	325	326	820	127	238	234	668
	NGS-based	169	195	195	771	132	148	148	591	207	283	298	682	121	121	121	433
	$\Delta_{SGT \rightarrow NGS}$ savings	87	170	175	267	− 7	8	35	138	14	42	28	137	6	116	113	234
Total cost including overheads ('000 €)	SGT-based	308	438	444	1245	151	188	221	875	265	390	391	983	152	285	281	801
	NGS-based	203	234	234	925	159	178	178	709	248	340	357	819	146	146	146	520
	$\Delta_{SGT \rightarrow NGS}$ savings	105	204	210	320	− 8	9	42	166	16	50	34	164	7	139	135	281

The main analysis results for each testing case are reported. In the first section, results are provided as cost per patient; in the second section, they are provided as overall results considering the total number of patients tested

aNSCLC advanced non-small-cell lung cancer, *CP* clinical practice, *mCRC* metastatic colon-rectal cancer, *NGS* next-generation sequencing, *pt* patient, *SGT* single-gene testing, *TMB* tumour mutational burden, $\Delta_{SGT \rightarrow NGS}$ variation in the transition from an SGT-based approach to an NGS-based approach

Table 2 Average number of tests per patient. Each path differs in terms of molecular alterations tested and testing frequency in the respective scenarios and in terms of testing techniques used, thus, resulting in a specific number of tests per patient

	Path 1: aNSCLC				Path 2: aNSCLC			
	Minimum set	CP	Future CP no TMB	Future CP	Minimum set	CP	Future CP no TMB	Future CP
SGT-based	5.2	6.7	7.2	8.2	4.6	5.2	5.6	6.7
NGS-based	2.1	2.1	2.1	2.1	2.1	2.6	2.6	2.6
$\Delta_{SGT \rightarrow NGS}$	3.1	4.6	5.1	6.1	2.5	2.6	3.0	4.1
	Path 3: mCRC				Path 4: mCRC			
	Minimum set	CP	Future CP no TMB	Future CP	Minimum set	CP	Future CP no TMB	Future CP
SGT-based	7.1	11.6	11.5	12.5	1.3	2.6	2.5	3.5
NGS-based	5.1	8.4	9.0	9.0	1.0	1.0	1.0	1.0
$\Delta_{SGT \rightarrow NGS}$	2.0	3.2	2.5	3.5	0.3	1.6	1.5	2.5

aNSCLC advanced non-small-cell lung cancer, *CP* clinical practice, *mCRC* metastatic colon-rectal cancer, *NGS* next-generation sequencing, *SGT* single-gene testing, *TMB* tumour mutational burden, $\Delta_{SGT \rightarrow NGS}$ variation in the transition from an SGT-based approach to an NGS-based approach

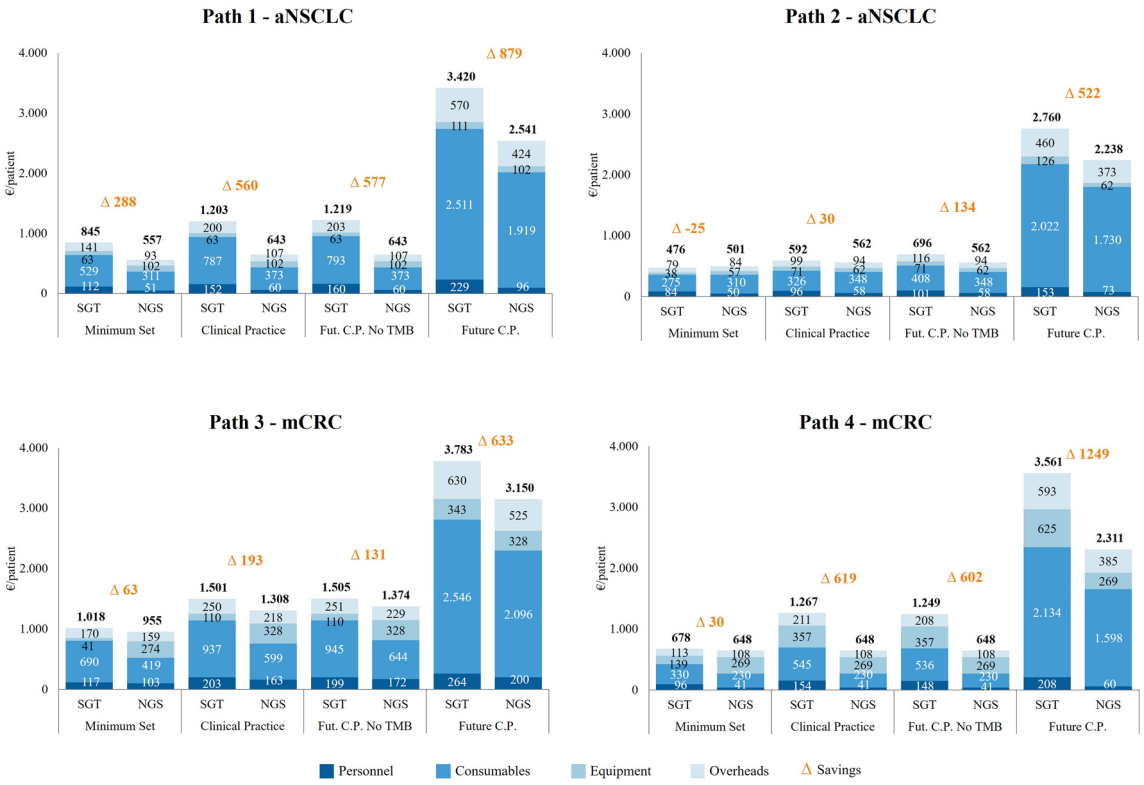

Fig. 2 Mean cost per patient. The mean cost per patient comparing the SGT-based and NGS-based approaches is shown for each testing case considering personnel, consumables, equipment (purchasing and maintenance), and overhead costs to perform all the required tests. *aNSCLC* advanced non-small-cell lung cancer, *CP* clinical practice, *mCRC* metastatic colon-rectal cancer, *NGS* next-generation sequencing, *SGT* single-gene testing, *TMB* tumour mutational burden

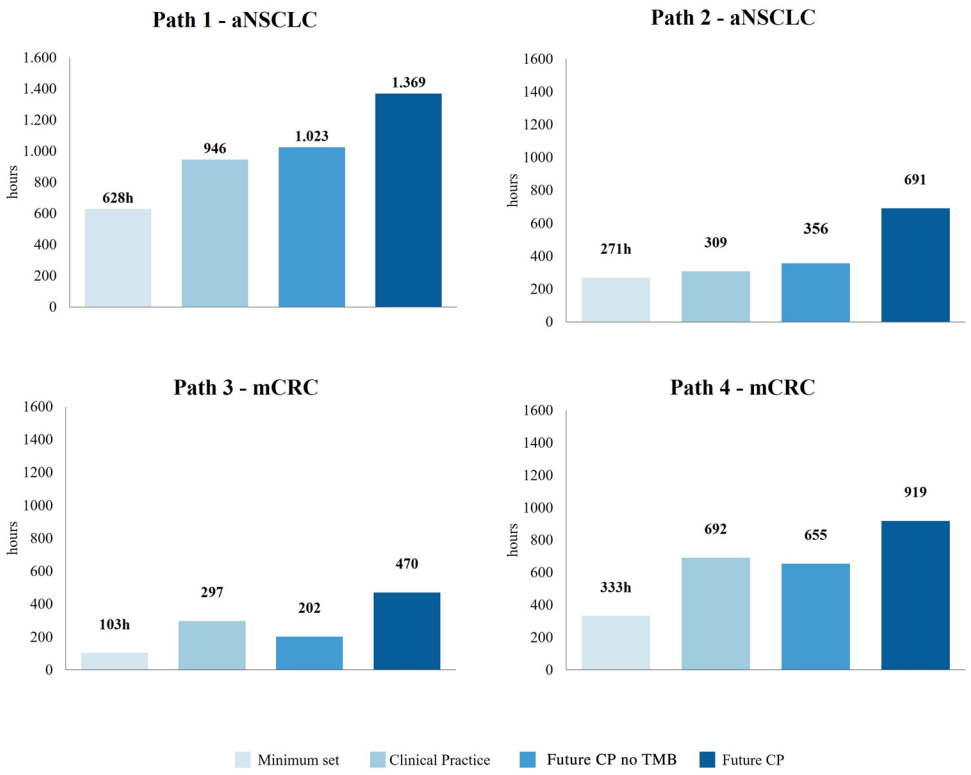

Fig. 3 $\Delta_{SGT \rightarrow NGS}$ overall personnel time savings. The overall personnel time savings generated by the NGS-based approach are shown for each testing case. *aNSCLC* advanced non-small-cell lung cancer, *CP* clinical practice, *mCRC* metastatic colon-rectal cancer, *NGS* next-generation sequencing, *SGT* single-gene testing, *TMB* tumour mutational burden

by the average personnel time spent performing all the tests required for a patient in the NGS-based approach.

Additional testable patients generated by the NGS-based approach ranged from 506, 142, 36, and 206 for paths 1, 2, 3, and 4, respectively, in the "minimum set" scenario, and a maximum of 923, 294, 56, and 397, in the "future CP" scenario.

3.4 Break-Even Analysis

The break-even volume represents the number of tested patients where the SGT-based cost per patient equals the NGS-based cost; above this threshold, an NGS-based approach generates savings.

Break-even charts for path 3 are presented in Fig. 4, while Table 4 illustrates the volumes and break-even thresholds for all paths. The larger the number of tested molecular alterations, the more the testing process can benefit from the NGS capacity to test a wider range of molecular alterations in a single run; the SGT-based approach would need to involve different techniques, hence requiring a higher number of tests. Table 4 shows that, moving from the "minimum set" to the "future CP" scenario, the patient break-even volume (if applicable) decreases and the NGS savings are easier to achieve.

3.5 Deterministic Sensitivity Analysis

Deterministic sensitivity analyses were performed for each path in the CP scenario, where all key parameters were varied by ± 20%. In all the paths, consumables costs (used for the Sanger technique in paths 1 and 3 and for NGS or mass spectrometry for paths 2 and 4) were the most impactful variable, as shown in Fig. 5. The variation within the determined range of the most impactful parameter (impact on $\Delta_{SGT \rightarrow NGS}$ savings is ±€39,183, ±€17,667, ±€26,760, and ±€16,200 for paths 1, 2, 3, and 4, respectively) caused the SGT-based approach to be slightly less expensive (€8215) than the NGS-based approach in path 2 only.

4 Discussion

The introduction of NGS has enhanced the potential detection of mutations, with an important impact on the diagnosis and treatment of many diseases. Although diagnostic procedures represent a small proportion of total pathway costs, growing attention has been paid to the impact of NGS on the budget and its cost-effectiveness compared to the standard single-testing approach. Three recent papers on economic studies on NGS have raised concerns on the way cost analyses have been carried out [4–6]. Furthermore, they revealed that the evidence on NGS costs is quite poor for Europe, and no data exist for Italy.

Table 3 Overall additional patients due to $\Delta_{SGT \rightarrow NGS}$ time savings

	Capacity increase (patients)			
	Minimum set	CP	Future CP no TMB	Future CP
Path 1—aNSCLC	506	786	852	923
Path 2—aNSCLC	142	119	164	294
Path 3—mCRC	36	43	27	56
Path 4—mCRC	206	321	294	397

Additional patients who could be potentially tested in each testing case if $\Delta_{SGT \rightarrow NGS}$ personnel time savings were used to increase the testing activity and if the NGS-based approach was adopted

aNSCLC advanced non-small-cell lung cancer, *CP* clinical practice, *mCRC* metastatic colon-rectal cancer, *NGS* next-generation sequencing, *SGT* single-gene testing, *TMB* tumour mutational burden, $\Delta_{SGT \rightarrow NGS}$ variation in the transition from an SGT-based approach to an NGS-based approach

The present study aimed to cover the information gap for Italy, investigating the costs of different diagnostic approaches (NGS-based vs SGT-based) in three Italian hospitals according to different scenarios characterized by an increasing number of mutations analysed. The current study was planned before the two systematic reviews were published. Notwithstanding, it was designed to address most of the limitations of previous studies that the two reviews highlighted. Our analysis compared different scenarios (dynamic approach) where NGS was gradually implemented and was not a virtual comparison between a full adoption of NGS and single testing. A microcosting approach was adopted because this approach is suggested if cost analyses are carried out in heterogeneous patients. We also detailed the cost items and methods used for estimation. Another advantage of the current study is that the mean cost per patient was estimated instead of the mean cost per test, to take into account possible double testing.

According to our estimates, the diagnostic mean cost per patient ranges from €501 to €3150 for the NGS-based approach and from €476 to €3783 for the SGT-based approach. Our results are comparable to those from most other studies relying on microcosting analyses and applied to cancer care. Two studies were conducted in the USA [25] and the Netherlands [26]. The relevant estimates included pre-analytics and analytics labour, equipment and consumables, bioinformatic data analysis, reporting, and overhead costs. Depending on the procedure used, the full assay cost per sample ranged between US$699 (€655 [27]) and US$2428 (€2275 [27]) in the USA and between

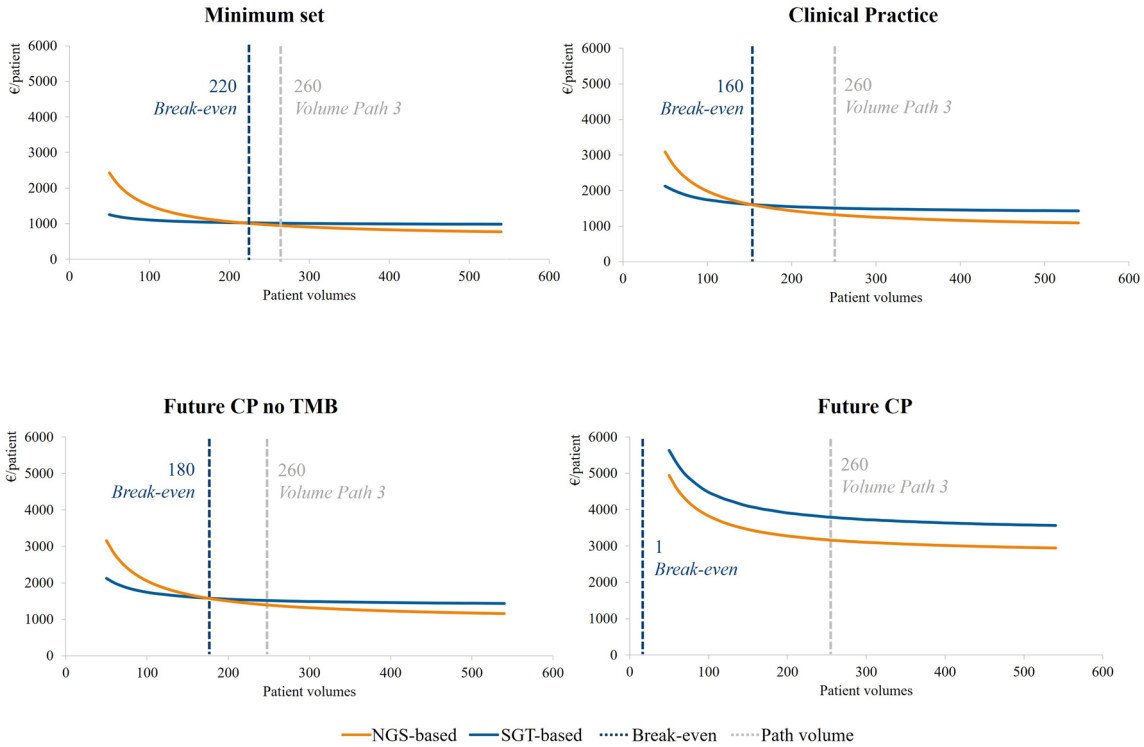

Fig. 4 Break-even analysis (path 3). The mean cost per patient for the SGT-based and NGS-based approaches in path 3 is displayed for each scenario and reported as a function of patient volume. The number of patients tested by the hospital ("volume path 3") and the threshold necessary for the NGS-based approach to generate savings ("break-even") are shown. *CP* clinical practice, *NGS* next-generation sequencing, *SGT* single-gene testing, *TMB* tumour mutational burden

Table 4 Break-even analysis volumes

Disease	Path	Hospital volume (patients/year)	Break-even volume (patients)			
			Minimum set	CP	Future CP no TMB	Future CP
aNSCLC	1	364	60	> 0	> 0	> 0
	2	317	–	70	> 0	> 0
mCRC	3	260	220	160	180	> 0
	4	225	180	> 0	> 0	> 0

The table illustrates, for each testing case, the break-even volume; "> 0" represents the NGS-based approach being less expensive for any number of patients tested

aNSCLC advanced non-small-cell lung cancer, *CP* clinical practice, *mCRC* metastatic colon-rectal cancer, *NGS* next-generation sequencing, *TMB* tumour mutational burden

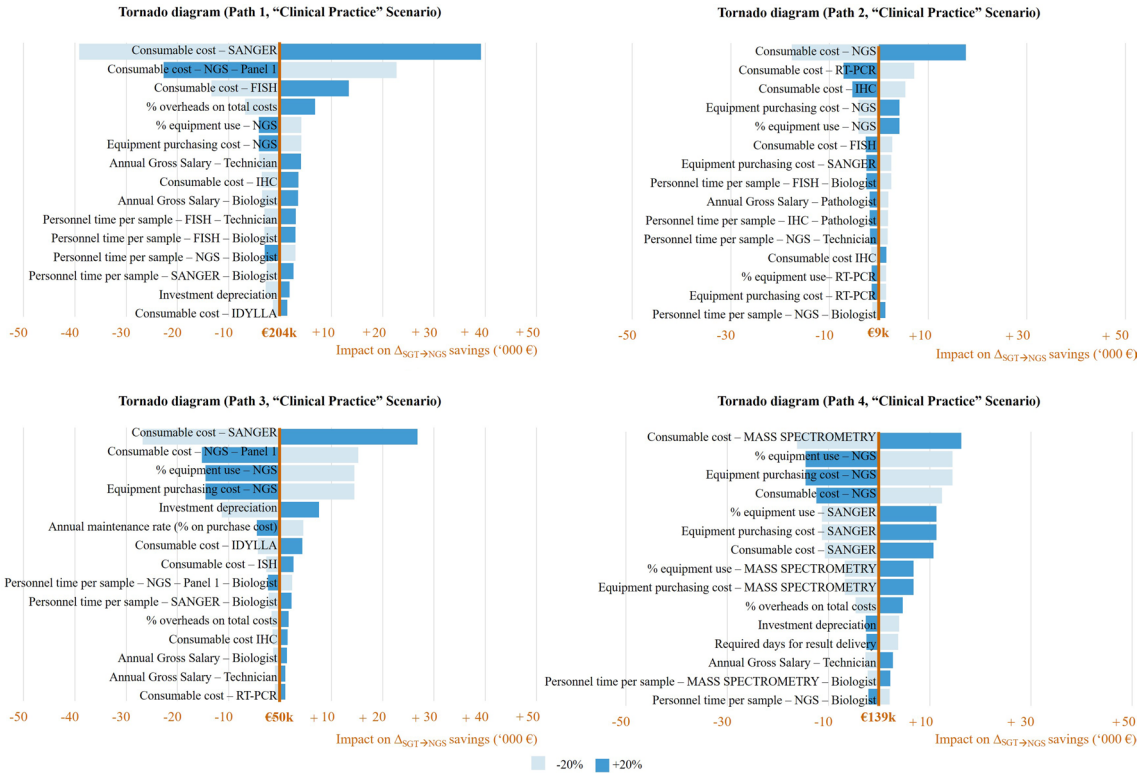

Fig. 5 Deterministic sensitivity analysis (CP scenario). The results of the DSA are shown in the CP scenario and are displayed in a tornado diagram (the 15 most impactful variables are included). Input data were varied (± 20%), and impacts on the $\Delta_{SGT \to NGS}$ savings were observed. *CP* clinical practice, *DSA* deterministic sensitivity analysis, *FISH* fluorescence in situ hybridization, *IHC* immunohistochemistry, *ISH* in situ hybridization, *mCRC* metastatic colon-rectal cancer, *NGS* next-generation sequencing, *RT-PCR* real-time polymerase chain reaction, *SGT* single-gene testing, *TMB* tumour mutational burden, $\Delta_{SGT \to NGS}$ variation in the transition from an SGT-based approach to an NGS-based approach

€606 and €2668 in the Netherlands. The Dutch study also assumed high productivity rates: 24 samples per test, one test per week, and 85% conclusive results (no additional tests required). Another recent study carried out in a single centre in the UK estimated the cost of genome sequencing for a cancer case equal to £6841 (€7754 [28]), £3420 (€3876 [28]) per genome. In all studies, consumables represent the most important cost item [24].

Our analysis reveals that by moving from the SGT-based to the NGS-based approach, hospitals can reduce sequencing

costs by €30–€1249 per patient depending on the scenario, and only in one testing case is the SGT-based approach less costly. The savings per patient tested are higher in scenarios with a more comprehensive set of molecular alterations tested. Hence, the higher the number of mutations screened, the more the NGS-based approach is less costly than the SGT-based one. This result was not surprising, since the SGT-based approach is less suitable when different alterations should be found. Another important result is that in all testing cases, the personnel time dedicated to sequencing is reduced, thus providing the opportunity to reallocate this saved time in other more labour-intensive activities.

Our research provides another interesting finding, i.e. the minimum number of patients needed to make the NGS-based approach less costly than the SGT-based one. The break-even point ranged from 0 to 220 depending on the complexity of the analysis, the hospital, and the disease (aNSCLC and mCRC). Other studies have shown only that the mean assay cost significantly decreased with higher volumes [26].

These findings have important implications for hospitals and regulators. There is clear evidence that using the NGS-based versus SGT-based approach is advantageous from an economic perspective, provided that a minimum number of patients are screened. This evidence should address the selection of centres accredited for providing NGS-based diagnostic procedures for the whole population.

Most of the other studies have estimated the cost per sample, which is useful for other purposes, i.e. comparing the economic efficiency of different laboratories or determining the fee for service payers should pay laboratories. Having estimated in our study the cost per patient may also help convert a fee-for-service-based funding system into a fee-for-episode-based funding system. A fee-for-episode-based funding system may push healthcare providers to better manage the whole sequencing/diagnostic process.

We are aware that the current study has some limitations. The microcosting analysis was applied to a small sample of research-oriented and teaching hospitals, which were selected on the grounds of their willingness to participate in the survey (sample of convenience). Although these hospitals cannot therefore be considered prototypical of Italian hospitals, these centres are likely to represent, in the future, accredited reference laboratories for NGS-based techniques. It should also be noted that two of the three studies relying on the microcosting approach mentioned before were carried out in one single centre [24, 26]. Another limitation of our study is that most of the input data were retrieved from interviews with healthcare professionals due to limited accessibility to other analyses (e.g. time and motion analysis for the time dedicated by each healthcare professional). However, confirmatory, repeated interviews were carried out to cross-check the robustness of the answers. Furthermore, we had to rely on benchmark data for those centres who did not provide all the required information (e.g. equipment purchasing costs and NGS consumables costs for path 2 and path 4) and on international published data for overhead costs, since data for the three centres were not available and there is no available evidence for Italy. Another limitation is the retrospective nature of the study; the most recent systematic review on health economics studies applied to NGS has recommended a prospective analysis [5]. Finally, this is a partial analysis comparing two alternative approaches (NGS-based vs SGT-based) in different scenarios from a cost perspective. This result should be integrated with process (e.g., diagnostic yield) and health (e.g., quality-adjusted life years) outcomes to have a complete set of information for decision-makers. A cost-effectiveness analysis was beyond our scope and would have required reliable data on the two sequencing strategies in all scenarios considered.

Despite these limitations, our study provides insights into the cost of NGS in Italian laboratories comprehensively testing mutations in aNSCLC and mCRC.

5 Conclusion

Although diagnostic procedures do not represent the most relevant cost of cancer patient treatment, they will increasingly play a central role in clinical decision-making. The optimization of diagnostic procedures is important for at least two reasons: (1) mutation-driven treatments have steadily increased in recent years, and (2) tumour-agnostic treatments based on molecular alterations occurring across a variety of different tumour types have been recently approved by the Food and Drug Administration (FDA) [29].

Along this line, our study showed that the NGS-based approach is less costly than the SGT-based approach, provided that a minimum number of patients are tested. This result can be considered for regulatory purposes, including the rules to accredit hospitals for NGS analysis, as well as for access issues (e.g., whether NGS can be covered by third-party payers), and finally for economic analysis, since NGS testing may accelerate the use of medicines and investment decisions.

We are perfectly aware that the decision to adopt an NGS approach should consider not only costs but also the effectiveness, organizational impact, availability of suitable treatments, its use in CP or in clinical trials, and data confidentiality issues, among other factors. Nevertheless, the present analysis aimed to generate evidence on one of the key drivers of decision-making in healthcare.

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Declarations

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Authors' contributions *Conceived and designed the research approach:* Giancarlo Pruneri, Filippo De Braud, Anna Sapino, Massimo Aglietta, Andrea Vecchione, Raffaele Giusti, Caterina Marchiò, Stefania Scarpino, Anna Baggi, Giuseppe Bonetti, Jean Marie Franzini, Marco Volpe, and Claudio Jommi. *Provided and validated the input data:* Giancarlo Pruneri, Filippo De Braud, Anna Sapino, Massimo Aglietta, Andrea Vecchione, Raffaele Giusti, Caterina Marchiò, and Stefania Scarpino. *Designed the analytical model and analysed the data:* Anna Baggi, Giuseppe Bonetti, Jean Marie Franzini, Marco Volpe, and Claudio Jommi. *Interpretation of the analysis:* Giancarlo Pruneri, Anna Baggi, Giuseppe Bonetti, Jean Marie Franzini, Marco Volpe, and Claudio Jommi. *Wrote the document:* Giancarlo Pruneri, Anna Baggi, Giuseppe Bonetti, and Claudio Jommi.

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