Cancer Dashboard for Italy - Access to Cancer Medicines

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Purpose and content

This report is a part of an international initiative aiming to facilitate the exchange of best practices in cancer care among European countries. The objective of the report is to describe the status of access to innovative cancer medicines in Italy with a focus on the Fund for Innovative Drugs. By illustrating how the Fund complements the existing Health Technology Assessment (HTA) of medicines and the overall healthcare system to improve patient access, this report also seeks to explore certain aspects that could be improved.

The description and analysis in the report relies on public information from national and regional authorities, recent publications, and interviews with three national experts – Dr. Francesco Perrone, president of the Italian Association of Medical Oncology (AIOM), Mr. Emanuele Monti, executive board member at the Italian Medicines Agency (AIFA) and former chairman of the Health Commission of Lombardy Region, and Ms. Anna Maria Mancuso, president of Salute Donna Onlus.

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Key summary

- Access to cancer medicines in Italy is very good in a European context, characterized by a high overall reimbursement rate of new medicines approved by the European Medicines Agency (EMA) and short time to reimbursement after EMA approval.
- The Fund for Innovative Drugs was established in 2017 and has become an integral part of the overall healthcare system and has been continuously enhanced over the years in terms of budget allocation and mechanisms of its use.
- Compared to other European countries with similar dedicated funds, the Fund in Italy seems to have the most sophisticated system of incentives related to ensuring timely access to innovative medicines.
- The number of drug-indications that are granted "innovative status" in Italy every year is significant, which favorably impacts the overall reimbursement rate and time to reimbursement in Italy.
- A considerable proportion of resources – around 15-35% - in the Fund remains unused almost every year.
- The Fund results in numerous benefits, including:
  - ✓ Timely patient access to innovative treatments.
  - ✓ More equal access across all regions.
  - ✓ Reduction of medicine spending in regional healthcare budgets.
  - ✓ Increased transparency and consistency of funding for innovative treatments and the overall HTA process.
  - ✓ Clear focus on the therapeutic value of new treatments.
  - ✓ Incentives for pharmaceutical companies to focus on innovation by rewarding significant clinical benefit (therapeutic value) of new medicines.
  - ✓ Stimulate research by making Italy attractive for investment in research activity.

Recommendations by the authors

Given the numerous benefits of the Fund in Italy, it is critical that policymakers uphold the Fund as an integral part of the overall healthcare system. Regular evaluations of the performance of the Fund should be conducted to identify opportunities for improvements and secure sufficient budget allocations in the future.

The main recommendation that the authors of this report put forward is to: "*Consider including drug indications with conditional innovative status in the Fund on similar terms as those with full innovative status, and use parts of the annual unused resources to finance drug indications with conditional innovative status.*"

Another recommendation by the authors of this report is to: "*Preserve incentives for pharmaceutical companies to focus on innovative areas of application throughout the entire life cycle of their products.*"

Governance of cancer care and pharmaceutical spending

The number of new cancer cases is on a continuous rise in Italy and in the European Union (EU). Until 2040, the number of cases is expected to increase by 19% in Italy and 17% in the EU (in terms of per 100,000 inhabitants) compared to 2022 (1). At the same time, almost 100 novel cancer medicines have been approved by the European Medicines Agency (EMA) over the last decade (2). The approval of new indications of previously approved medicines to new or wider patient populations has also increased. For instance, in 2020, the EMA approved 17 new indications in oncology in comparison with 10 new oncology medicines (3).

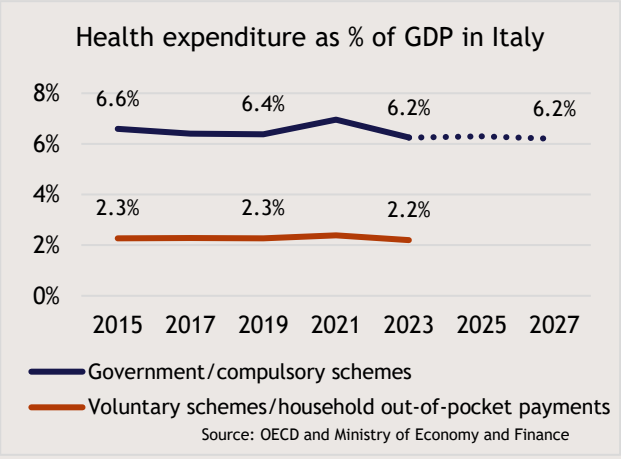
The opportunity new innovations bring to improve patients' outcomes is dependent on healthcare systems' ability to appraise, fund, and adopt new treatments in clinical practice to make them accessible to patients. Although most countries have increased their total health expenditure over the last two decades, the share of healthcare resources devoted to cancer have mostly remained stable over time at around 6% (3). Moreover, access to innovative medicines varies considerably between EU countries and potentially even within countries (4, 5). Apart from the ability of countries to fund new innovative treatments, national pricing and reimbursement policies (including health technology assessment, HTA) are often cited as a significant barrier to timely access to innovative treatments (5, 6).

At the EU level, political commitment has been achieved to improve cancer care with the launch of the Europe's Beating Cancer Plan (EBCP) in 2021 and the EU Cancer Mission under Horizon Europe 2021-2027 (7, 8). In terms of HTA specifically, the recent adoption of the EU HTA regulation that enters into force on January 12, 2025 marks a new future for joint HTA in the EU with the promise of ultimately providing faster access to innovative treatments across the EU (9).

Healthcare system and financing in Italy

The Italian National Health Service, the Servizio Sanitario Nazionale (SSN), has in recent decades undergone a process of decentralization, which is now one of the main characteristics of its structure and functionality (10). Today the SSN is organized into three levels: national, regional and local and the responsibility for health service delivery is shared between the central government and the country's 21 regions and autonomous provinces. The SSN offers universal healthcare coverage, and the central government is responsible for defining the national benefits package, known as the Livelli Essenziali di Assistenza (LEA), ensuring equitable distribution of resources to regional health systems, and overseeing their management (10). Regional authorities have a high degree of autonomy as most of the legislative and executive powers are delegated to the regional level of governance. Regions are responsible for financing, organizing, and delivering healthcare services locally through local health authorities (Aziende Sanitarie Locali, ASLs[1]) according to health objectives specified at the national level.

Overall, the total health expenditure (from both public and private sources; not cancer specific) has remained relatively stable at just below 9% of GDP over the last decade (11). The share of public health expenditure was 6.2% of GDP in 2023 and it is projected to reach 6.4% in 2024 and 6.2% in 2027 (12). Recent national expenditure data suggest that the planned allocation of resources to the SSN will further expand the already existing gap between available resources and actual needs of the Italian population (13). Private health expenditure has been growing over the last decade and was reported to be at 26% of total health expenditure in 2019. Out-of-pocket (OOP) expenditure represented the largest share (89%) of private health expenditure.



Italy has a well-established social security system that provides economic benefits (upon request) to all workers if their working capacity is reduced or absent due to physical or mental illness (14). To put this into perspective for cancer, one study that evaluated the social and economic costs of breast cancer in Italy reported that these benefits amounted to an average annual expense of over €257 million (14).

[1] The ASLs are public and independent entities that deliver services either through their own facilities or via contracts with private providers.

Governance of pharmaceutical spending in Italy

In 2022, the overall pharmaceutical expenditure (both public and private) amounted to €34.1 billion, with an increase of 6% compared to 2021 (15). Data from the Italian Medicines Agency (AIFA) for 2019 show that around 76% of all pharmaceutical expenditure are reimbursed by the SSN whereas the remaining part is paid OOP (10).

Since 2007, Italy has practiced compulsory payment policies for pharmaceutical companies to support regional expenditures, which contributes significantly to the region's overall budget capacity (16). There is a maximum annual spending limit for drugs by the SSN and mandatory payback of any over-run (in whole or in part) by the pharmaceutical companies. In fact, from 2013 to 2021, the overall payments to the SSN have doubled in relation to the payback the regions receive from SSN to cover drug expenditure (16). The governance of national pharmaceutical expenditure lies within AIFA's responsibility. The agency makes use of four main instruments (17):

- Ceilings for outpatient and inpatient SSN pharmaceutical expenditure
- Monitoring of pharmaceutical expenditure on an annual basis
- Defined budget for each marketing authorization holder (MAH) to be used for potential paybacks.
- Paybacks to the regions after exceeding the pharmaceutical spending ceiling.

The main payback mechanisms in place are as follows:

- A 5% reduction on the public price including VAT of medicinal products reimbursed by the SSN (Regulated by Law 27 December 2006, n. 296 (Financial Law 2007)) (18). 50% of it are used to fund orphan medicines and life-saving medicines that have not yet been authorized in Italy, the remaining part goes to funding independent research (19).
- "Payback 1.83%" was introduced according to article 11 of the Legislative Decree 78/2010. This payback entails a payment to the Italian regions which corresponds to 1.83% of the public price of their medicinal products provided by the SSN that is sold via the retail system (18, 20).
- Payback Law 222/2007 and Law 135/2012 (Balancing of the Pharmaceutical Expense). At the beginning of the year, AIFA sets a budget for each pharmaceutical company. This budget is calculated based on the previous year's recorded volumes and is divided into categories for equivalent and patented drugs (20). The mechanism states that, in case of the overshoot of the ceiling of the national pharmaceutical expenses, pharmaceutical companies need to balance this through the payment to the Italian regions. In 2021, the overall spending ceiling for pharmaceuticals was at 14.85% of the total SSN budget, with 7% for spending in community pharmacy and 7.85% for spending at hospitals done through direct purchases of regions (20). These spending ceilings are essentially always exceeded at the hospital level (21), with the result that pharmaceutical companies need to pay 50% of this exceeding amount back to the regions based on their respective market shares (20). The exact payback amounts are determined by AIFA for each company.

Key policies and initiatives relating to improving access to medicines in Italy

In Italy, the government defines health policy strategies through a process which is carried out in collaboration with the 21 regions (10). The main policy document in relation to cancer care is the National Oncology Plan 2023-2027 which was adopted in January 2023 (22). It includes key objectives and strategies aligned with the EBCP to be implemented by the regions and autonomous provinces (2). It encompasses all areas of cancer care from prevention (primary, secondary and tertiary), early detection and diagnosis to treatment and survivorship. The plan is a framework to guide regions in their work to address disparities in the accessibility and quality of cancer care both within and between regions. In the context of treating patients with cancer, a significant part of the plan describes the need of a uniform organizational structure across the country that integrates hospitals with outpatient care and promotes a systematic approach of using multidisciplinary teams and molecular tumor boards in so called "oncology networks" (7). In terms of access to treatments, the plan emphasizes the importance of equal access for patients, specifically for innovative products in all regions. Another related objective is to complete the establishment of the National Cancer Registry and support innovative oncological research activities. However, specific strategies and objectives around this topic are lacking in comparison with other areas of treatment (improving organizational structure, the use of biomarker testing, training of healthcare professionals etc.).

Moreover, Italy was one of the founders of the "Valetta Declaration" in 2017, which is a cross-country collaboration on HTA that advocates for affordable access to medicines through solidarity, collaboration, and transparency (23). Italy has also been one of the key promoters of the World Health Assembly resolution "Improving the transparency of markets for medicines, vaccines, and other health products" from 2019, which resulted in an updated legislation on increasing price transparency in the pricing and reimbursement negotiations in 2020 (19).

The establishment of the Fund for Innovative Drugs in 2017 and its continuous evolvement over the years marks another significant measure to finance and improve access to innovative medicines in the country. Apart from the Fund, additional policies by AIFA exist to promote early access to innovative medicines, as shown in the table below.

Policy/initiative	Description
Horizon scanning activities	AIFA conducts horizon scanning activities to systematically identify and prioritize new, upcoming or already existing health technologies on the market. The objective is to plan for future HTA needed and allocation of economic resources to the SSN (24).
Early-access schemes	Free access to medicines can in some case be allowed before national marketing authorization or, for medicines already authorized, for indications other than those for which the medicinal product has been authorized in Italy (off-label use) (25). Examples of early access routes are: • Compassionate use - Involves direct and free delivery of the medicine by the manufacturer (25). For life-threatening diseases, free-of-charge access can be requested to manufacturers, under AIFA supervision, even to unapproved agents based on available phase 2 evidence (Decree 8/5/2003) (25, 26). Reimbursement of drugs for diseases with unmet need require further data collection to inform HTA (Law 648/96) (26). • AIFA National Fund (Law 326/2003 – "5 % fund"). • Non-repetitive use of advanced therapies in urgency and emergency situations (25).
Managed entry agreements	Managed entry agreements (MEAs) are contractual agreements between the payer (or HTA body) and the pharmaceutical company that stipulates specific terms and requirements on the price and conditions for the treatment to be reimbursed. There are numerous types of MEAs, but most EU countries rely on price discounts. Italy was one of the first countries to use MEAs, and it is one of the countries with the highest number of contractual agreements (19). One study found that access to oncology drugs in Italy is shorter if an MEA is in place compared to not having an agreement (27).

Another measure at the regional level is pooled procurement, which involves joint purchase agreements through a permanent procurement body or a collaborative agreement (25). Evidence suggest that pooled procurement has contributed significantly to lower drug prices, enhanced governance and transparency (25). In Italy, one study found that pooled procurement of drugs by several regions is particularly beneficial where the institutional quality is lower (28).

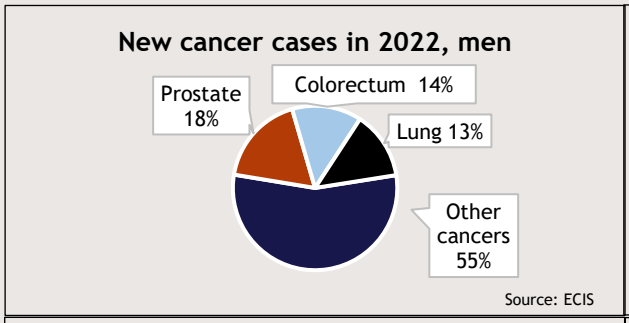
Disease burden of cancer

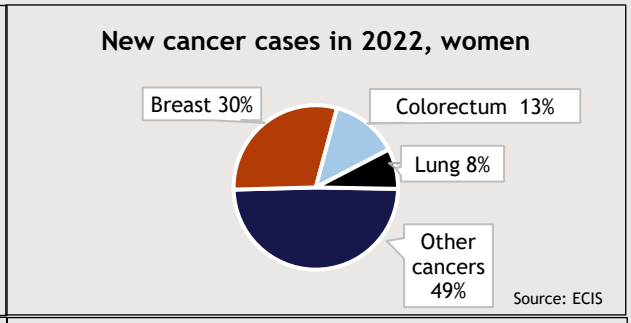
According to estimates by AIOM, 395,000 new cancer cases were estimated to have been diagnosed in Italy in 2023, 208,000 new cases in men and 187,000 in women (29). The three most commonly diagnosed cancer types in men in Italy are prostate cancer, colorectal cancer and lung cancer, and in women breast cancer is followed by colorectal cancer and lung cancer (1).

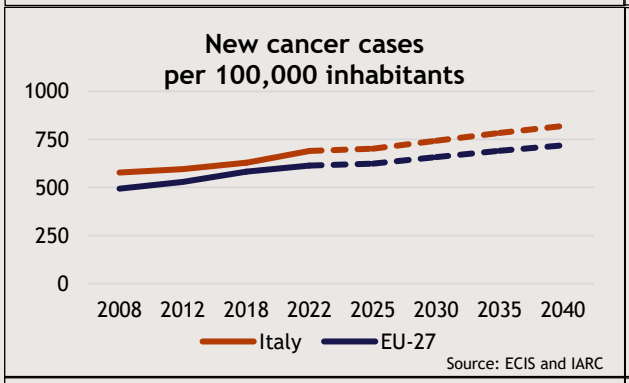
Year 2022	Italy	EU-27
Life expectancy at birth (years) (Source: Eurostat)	82.8	80.6
New cancer cases (estimated) (Source: ECIS)	407,240	2,742,447
New cancer cases per 100,000 (estimated crude rate) (Source: ECIS)	690	614
Cancer deaths (estimated) (Source: ECIS)	192,227	1,292,600
Cancer deaths per 100,000 (estimated crude rate) (Source: ECIS)	326	289

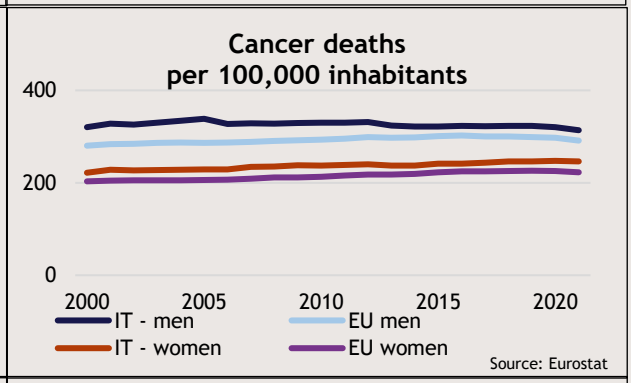
Over the last two decades, the estimated number of new cancer cases in Italy has always been above the EU average (between 17% to 8% in 2008-2018) (1, 30-32), most likely a reflection of the older age structure of the Italian population. The continuous increase in cancer cases overall in Italy is particularly highlighted in the latest "i numeri del cancro in italia" report (year 2023) by AIOM (29). Over the next two decades, the absolute annual number of new cancer cases in Italy is expected to further increase, on average by 1.3% per year in men and by 0.6% per year in women (29). This follows closely the overall development expected in the EU (1), and is mostly driven by population aging.

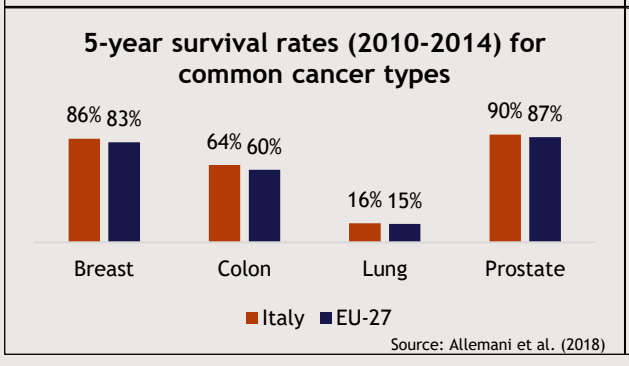
The number of cancer deaths per 100,000 inhabitants was 8% higher for men and 11% higher for women than the EU average in year 2021 (based on crude rates) (33). However, based on age-standardized mortality rates, the mortality has decreased for all main cancers except pancreatic cancer during 2011-2019 (34). According to AIOM, around 268,000 deaths were estimated to be avoided between the years 2007 and 2019 (based on a prognosis of expected deaths by using mortality rates between 2003 and 2006) (29). The survival rates in Italy for the most common cancer diagnosis (based on data from year 2010-2014) were slightly above the EU average (35). The survival rates are on a positive trend and have improved compared to the earlier diagnosis period in 2000-2004 (35).

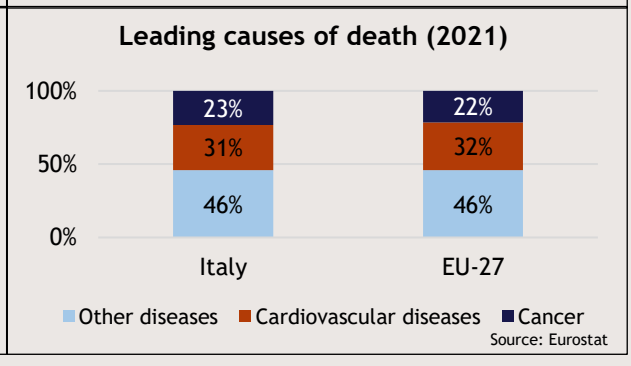












Economic burden of cancer

In Italy, the estimated overall economic burden of cancer amounted to €343 per capita in 2018 (36). Most of the burden is caused by healthcare expenditure (50%) and the remaining part is caused in equal parts by the loss of productivity of working-age patients and informal care (both 25%). In fact, Italy has the largest informal care costs related to cancer care in the EU (36).

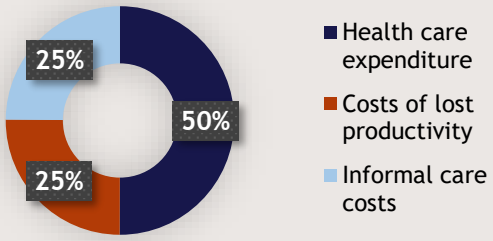
The economic burden of cancer consists of:

Healthcare expenditure (direct costs):
- Resources of the healthcare system (medical equipment, staff, medicines, etc.) funded both by public and private sources

Costs of lost productivity (indirect costs):
- Productivity losses from sickness absence, permanent incapacity/disability, and premature mortality of working-age patients

Informal care costs:
- Value of the time forgone by relatives and friends to provide unpaid care

Composition of the economic burden of cancer in Italy in 2018



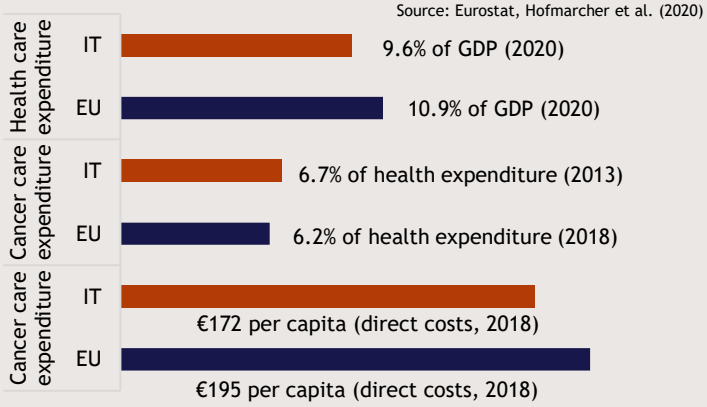
Source: Hofmarcher et al. (2020)

The economic burden of cancer (excluding informal care costs for which no trend data are available) has been relatively stable around €250 per capita between 2000 and 2018 (in 2018 prices) based on estimates from previous work published by the Swedish Institute for Health Economics (IHE), see graph below (36).

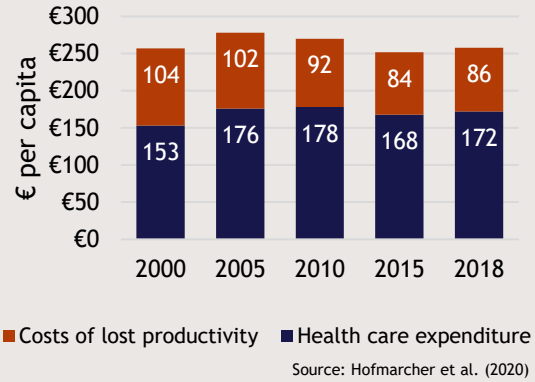
The exact amount of total health expenditure that are spent on cancer care are unknown in Italy. A previous study published in 2013, stated a share of 6.7% that is spent on cancer care (€7.5 billion out of €110 billion in total health expenditure; the exact year was not specified) (37). In 2018, the cancer expenditure were estimated to have reached €10.4 billion with €4.5 billion being spent on cancer medicines (based on list prices and without taking into account discounts and clawbacks) (34, 36).

Healthcare and cancer care expenditure

Source: Eurostat, Hofmarcher et al. (2020)



Economic burden of cancer in Italy (in € per capita)



Source: Hofmarcher et al. (2020)

A study by Altini et al. (2020) analyzed the cancer care cost in 2016 for several cancer types in (n = 10,486) based on data from clinical records from The Romagna Cancer Institute and total health expenditure data from the Italian National Statistical Bureau (38). The cancer care costs as a share of total health expenditure amounted to 11% that year and the authors noted that these findings were higher in comparison with previous national estimates. However, there are difficulties with generalizing these results due to the large regional differences in healthcare spending that exist in the country (39).

In terms of future investment, Italy will use part of the EU Recovery and Resilience Facility - with a total national budget of €194 billion - to improve cancer care in the coming years (40).

Availability of new cancer medicines

The local availability of new medicines is defined by the European Federation of Pharmaceutical Industries and Associations (EFPIA) as the inclusion of a centrally approved medicine by the European Medicines Agency (EMA) in the national/regional public reimbursement list (4). Every year, EFPIA publishes a report, the EFPIA WAIT Indicator Survey, which monitors the local availability of recently approved medicines.

The local availability of new cancer medicines with approval by the EMA differs considerably between EU countries (4). Many causes for delays and unavailability of new medicines at the country level have been identified across the EU (5), such as (i) limited public budgets for medicines, (ii) late company submission or late start of the national pricing and reimbursement process, (iii) lack of clearly defined timelines for pricing and reimbursement, (iv) the complexity of the HTA process.

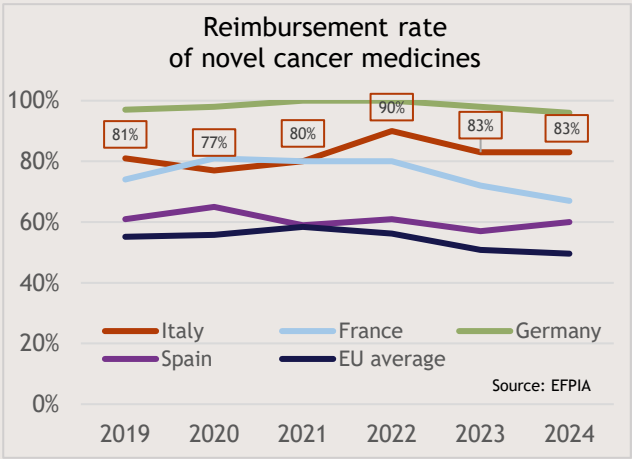
At the EU level, a revision of the EU pharmaceutical legislation is underway. One objective is to reduce country differences in the availability of new medicines and to shorten the time from EMA approval until patient access (41). In addition, the new EU HTA regulation will apply for cancer medicines and advanced therapy medicinal products from January 12, 2025. This will entail a joint (cross-country) clinical assessment of the relative effectiveness of new medicines (42).

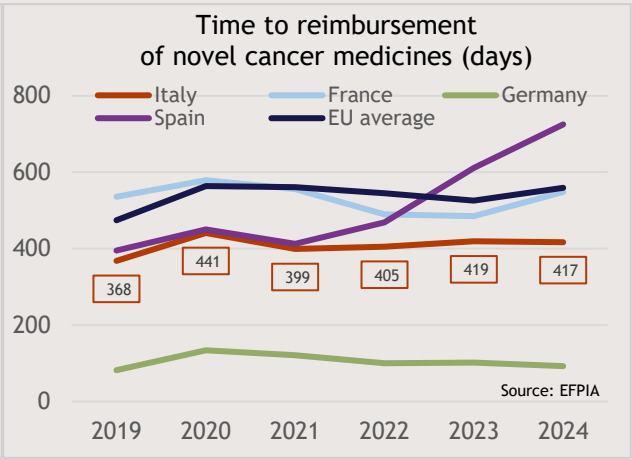
Availability in Italy

The reimbursement rate for new cancer medicines (with EMA approvals in 2019-2022) was 83% in Italy in 2024, putting Italy far above the EU average, as in previous years (4). With the exception of Germany, which provides temporarily reimbursement to all new treatments approved by EMA (96% reimbursement rate in 2024), Italy has a higher reimbursement rate than both France (67%) and Spain (60%). According to Dr. Perrone, there is only a minor proportion of the drugs approved by the EMA that later do not receive a reimbursement in Italy (around 3-4%). The high reimbursement rate in Italy indicates that the HTA system and its related processes are reliable and able to ensure that new cancer medicines are evaluated and reimbursed.

The reimbursement time from EMA approval to local reimbursement in Italy was on average 417 days in 2024, which was shorter than the EU average of 559 days (4). However, according to Dr. Perrone, 417 days is still longer than the expectations from HTA stakeholders and patients. Six EU countries have a faster reimbursement procedure than Italy: Germany, Denmark, Austria, Netherlands, Finland, and Sweden. The average reimbursement time in France and Spain was 548 and 725 days, respectively. The relatively short time to reimbursement of novel cancer medicines indicates that the processes at AIFA are effective compared to other EU countries.

According to Dr. Perrone, there is a trade-off between achieving a high reimbursement rate and a short reimbursement time in each HTA system. The fact that Italy performs relatively better in terms of ensuring the availability of new drugs rather than having the fastest processing time, seems appropriate. Indeed, the results as depicted in the figures below should have a high impact on patients' ability to access oncology drugs in Italy. However, the EFPIA WAIT indicator survey does not give a full picture on the regional differences in access to novel cancer medicines in Italy (see the next section on regional HTA for more details) and it only looks at new medicines (and their first indication) rather than at all new indications approved by the EMA.





In comparison with most other EU countries with established HTA systems, Italy is unique by having both a national and a regional HTA system for new medicines (43). This means that for a new treatment to become reimbursed and available to patients in all 21 regions, the pharmaceutical company must successfully gain access both on a national level and by all regional authorities.

National HTA in Italy

The Italian Medicines Agency (AIFA) is the government agency responsible for both national regulatory approval, pricing and reimbursement assessment on a national level for both outpatient medicines (prescription based) and inpatient medicines (used within hospitals). As early as in 1997, pharmaceutical companies needed to provide health economic evidence for the HTA process in Italy (44). However, the first official guidelines for economic evaluation of new medicines were published no earlier than in 2020 by AIFA (44).

The assessment process starts with a submission from a pharmaceutical company with appropriate documentation and health economic evidence in line with criteria stipulated by AIFA (45). The evaluation of the submitted health economic evidence by AIFA is extensive and includes the following steps (46):

- ✓ critical evaluation of the pharmacoeconomic and clinical studies
- ✓ revision of the pharmacoeconomic model
- ✓ literature review for the identification of further published pharmacoeconomic studies
- ✓ identification of recommendations and decisions taken in other countries concerning the medicinal product under application
- ✓ analysis of treatment costs compared to therapeutic alternatives
- ✓ economic-financial impact assessment

If the presented evidence is found acceptable, the price is then negotiated between AIFA and the company. Following a positive outcome of these negotiations, the drug is included in the positive reimbursement list (Prontuario Farmaceutico Nazionale, PFN). In addition, AIFA can decide to put prescription restrictions on certain medicines or therapeutic classes, which are known as “AIFA note” (47). There are exceptions to the main evaluation process for certain novel medicines, e.g. in the case of early-access schemes as explained in previous sections.

The evaluation process by AIFA was until recently carried out by two scientific committees, the Technical and Scientific Committee (CTS) and the Pricing and Reimbursement Committee (CPR). As of January 30, 2024, a governance reform of AIFA replaced CTS and CPR with a new committee called the Scientific and Economic Committee for Medicines (CSE), responsible for assessment of new technologies (48, 49). As of today, little is publicly known as to what changes in the HTA processes this new reform will result in. According to Mr. Monti, one aim of the reform was to address the time until a patient gets access to a new therapy, but also to ensure that the decision is based on a scientific assessment of the therapeutic benefit and an economic assessment. What is also known is that the CSE includes 10 members, which is half the number of the previous CTS and CPR.

As described above, the average time until a new oncology drug is included in the national reimbursement list in Italy is 417 days according to the latest EFPIA WAIT indicator survey from 2024 (4). Apart from the assessment time by the national HTA agency (in this case AIFA), this also includes the time from the market authorization by the EMA until the market authorization holder (MAH) decides to apply for reimbursement. However, it is also possible for AIFA to start the assessment after the CHMP[2] recommendation (before the final EMA decision) (6). According to the latest published AIFA report on time to authorization of pharmaceutical pricing and reimbursement procedures, the overall duration of procedures decreased from 2018 to 2020, from an average of 9 to 8 months for non-generic medicines (not oncology specific) (50). However, there is also a time delay by AIFA when sending out the final decision for publication in the Official Gazette, which on average took 2 months for non-generic medicines in 2020 (50). For medicines of exceptional therapeutic/societal benefit and orphan drugs, the assessment time by AIFA should not exceed 100 days (26).

In addition to AIFA, there are other national bodies that support the healthcare system with HTA and collaboration between the state, the regions and autonomous provinces, namely the National Center for Health Technology

[2] The Committee for Medicinal Products for Human Use of the EMA.

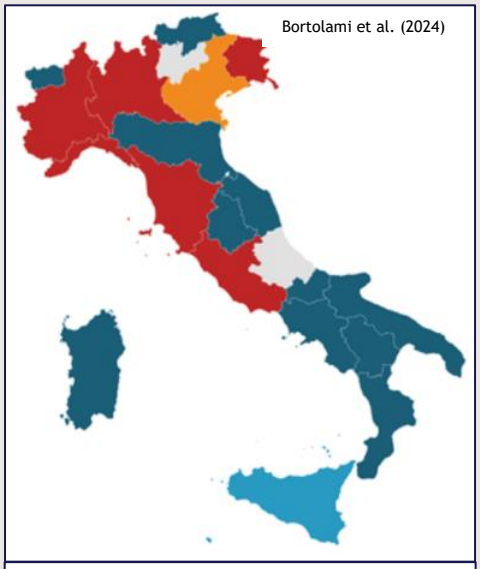
Assessment (part of the National Institute of Health, ISS) (51), and the National Agency for Regional Healthcare Services (AGENAS) (52).

Regional HTA in Italy

After reaching a positive decision by AIFA, companies commonly need to pursue regional market access activities (including HTA and price negotiations) to ensure that new treatments are finally reimbursed. At the core of these regional HTA processes are the so called "regional drug commissions" (also referred to as local therapeutic commissions) with the responsibility to decide what drugs should be included in regional formularies (also knowns as local reimbursement lists or Regional Hospital Therapeutic Handbooks) (19). These regional formularies were originally intended as a non-binding regional list of all drugs used in regional hospitals. However, over time the reimbursement limits imposed on the regions for exceeding expenditure caps has turned them into a binding list. According to Dr. Perrone, the regional HTA processes are in many ways redundant as they repeat assessments already performed at the national level by AIFA. Furthermore, by allowing regions to have their own criteria for regional access, it contributes to regional inequalities in access to novel treatments. According to Mr. Monti, AIFA and the regions need closer communication about the scientific reports. Currently, there are silos in the system. Some regions might restart the whole HTA process, and they evaluate aspects that the EMA and AIFA already have evaluated. The main recommendation is to have a stronger dialogue between AIFA and the regions to cut time and administrative processes. AIFA is working on this right now.

In comparison with the national HTA process, the regional HTA includes a more direct budget perspective, as the decision makers are responsible for keeping pharmaceutical expenditure in line with budgetary targets. Another important aspect is that regions can also decide to implement other related policies to ensure cost containment, such as procurement policies and actions on prescribing behavior when they stipulate the prescribing criteria for the pharmacies (53). Regional drug commissions can effectively block the prescription of a drug that is theoretically prescribable nationwide in Italy after AIFA approval (54).

In addition, drug evaluations and decisions on reimbursement at the regional level are not uniform across the country. A recent study by Bortolami et al. (2024) investigated to what extent regional formularies are used in Italy and found large regional differences (55). Out of 19 regions that responded to the survey in the study, six regions reported that they do not use regional formularies or regional drug commissions (marked as red in the figure to the right). According to the authors, a reason why certain regions do not have these is to ensure that drugs are immediately available in the region after it is included in the national reimbursement list (55).



Red = No drug formulary (RF) or therapeutic drug commission (TDC)
Orange = TDC but not RF
Dark blue = RF and TDC
Light blue = RF but no TDC
Grey = no information

A recent study found that the time to regional access varies considerably between Italian regions (56). The study assessed the time from the date of publication in the Regional Official Journal (GURI)[3] until the end of the tendering process and found that it took on average 112 days for new active substances to reach regional access (min: 1 day; max: 773 days) based on data covering the years 2019-2022. Another study investigated specifically what factors contribute to regional differences in time to access (57). Apart from whether a drug has an innovative status or not (see next page), the study found that non-orphan drugs (compared to orphan drugs) and combination therapies (compared to monotherapy drugs) were associated with a longer regional access time in seven out of ten regions and eight out of ten regions included, respectively (57).

[3] Once a new drug is approved in a region it is included in the Regional Official Journal (GURI), and immediately thereafter inserted in the regional formulary.

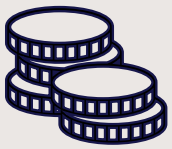
Fund for Innovative Drugs

The Fund for Innovative Drugs (*Fondo per i Farmaci Innovativi*) - originally consisting of two but now merged into a single fund – was established in April 2017 as means to improve access to novel innovative medicines in Italy (58). According to Dr. Perrone, the establishment of the Fund was a measure to secure funding for cancer treatments, which was inadequate at that point in time. Ms. Mancuso noted that the establishment of the Fund was an achievement of a group of associations under the coalition 'Health: a Good to be Defended, a Right to be Promoted' coordinated by Salute Donna ODV. The request for the establishment of the Fund stemmed from the fact that not all patients had equal access to innovative drugs. There were significant disparities in treatment across different regions, leading to substantial differences in cancer care between patients. The underlying cause was that regional budgets were constrained by caps, and regional policies varied in terms of priorities and health investment strategies.

AIFA is the government body that assesses which new medicines should be covered by the Fund. Based on their level of innovation, medicines are classified into three groups – "fully innovative", "conditional innovative", and "not innovative". Drugs with full and conditional innovation status are directly included in the regional formularies and consequently directly prescribable. The regional drug commissions cannot block their inclusion in the regional formularies. As noted by Dr. Perrone, the mechanism of the Fund in terms of fast-tracking regional access with a national assessment by AIFA goes in the opposite direction of the political system that today promotes regional autonomy. According to Mr. Monti, there are big differences between the regions in terms of organization and culture. The Fund bridges some of these differences and helps the regions to be quicker and skip some barriers, resulting in faster patient access after EMA approval. Nevertheless, there is a need to preserve the regional identity, because different regions have different/special needs, as maintained by Mr. Monti.

The Fund is financed on the national level, thereby offering indirect financial support to the regions and their regional healthcare budgets for medicines. Annual payouts are made to the regions in proportion to the amount spent on innovative drugs in the previous year. Any deficit or surplus of these allocations are monitored and regulated rigorously in annual budget processes (59). More specifically, data on spending on innovative drugs (based on actual sales prices) are listed in national and regional pharmaceutical expenditure monitoring documents which are continuously updated by adjusting for annual paybacks by pharmaceutical companies to the regions and linked to agreements of conditional reimbursement or outcome-based agreements (59). It should also be noted that the resources allocated to the Fund are excluded from the calculation of pharmaceutical expenditure at the hospital level and, therefore, do not contribute to any possible overshooting of the ceiling of 7.85% of the total SSN budget for pharmaceutical spending at hospitals.

Evolvement over time



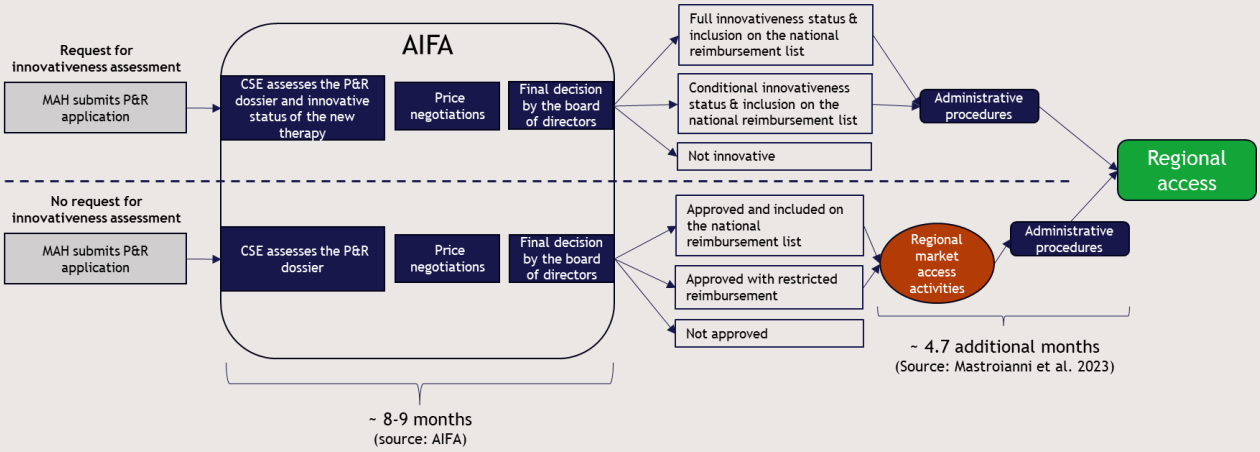
Between 2017 and 2020, the Fund consisted of two separate entities, one part worth €500 million dedicated to innovative oncology drugs and another part worth €500 million for other innovative drugs. In 2021, the two separate entities were merged into one single fund for all innovative drugs worth €1 billion (60). From 2022 onwards, the budget of the Fund increased with €100 million per year, reaching a total of €1.3 billion in 2024 (61). According to Dr. Perrone, the Fund is sustainable and cannot fail, as a dedicated amount of financial resources is allocated to it each year.

Initially, AIFA granted the innovative status on a product basis for a medicine. This was changed in 2018 to instead focus on a specific indication, meaning that a medicine with multiple indications can have both innovative indications and non-innovative indications at the same time (60).

Assessment of innovation status

AIFA assesses and decides on the inclusion of new medicines in the Fund. The assessment is based on the indication approved by the EMA. In practice, the assessment of innovative status is conducted in parallel with the pricing and reimbursement application upon request by the pharmaceutical company. The figure below illustrates this process, where a full innovative status from AIFA gives the drug-indication immediate access to the regional formularies, with the costs of the medicine for the hospitals being fully refundable by the Fund.

Simplified illustration of the HTA processes from national reimbursement application to regional access in Italy



Notes: MAH = Market authorization holder, P&R = pricing and reimbursement, CSE = Scientific and Economic Committee for Medicines.

The AIFA criteria for assessing a drug's innovation status are described in the table below. In this assessment, a drug can either be classified as fully innovative, conditional innovative, or not innovative. The final decision by AIFA is based on a grading system of the overall ranking of the levels across the three criteria listed in the table below. Prior to the assessment process, the company needs to submit a specific form to request recognition of innovation in which the company has to describe the evidence that supports and justifies the levels of ranking (62).

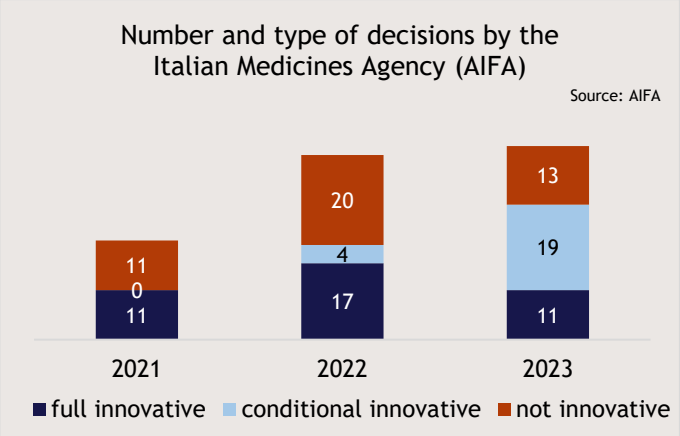
Assessment criteria	Levels of ranking[3]				
1. Therapeutic need	Maximum[1]	Important	Moderate	Poor	Absent
2. Added therapeutic value	Maximum[2]	Important	Moderate	Poor	Absent
3. Quality of clinical evidence[3]	High		Moderate	Low	Very low

[1] No alternative therapeutic options available. [2] Greater efficacy than alternative therapeutic options (if available) in clinically relevant outcomes, ideally curing the disease or altering its natural history. [3] AIFA uses the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system to assess the quality. See Appendix for a more detailed description of each level.
Source: Fortinguerra et al. 2021 (58)

A study by Fortinguerra et al. (2021) analyzed the importance of each criterion in the assessment of innovativeness in 2017-2021. They found that a ranking of "important" added therapeutic value was most frequently observed among drugs that were granted full innovative status and that all drugs with a conditional innovative status had a "moderate" added therapeutic value (58). A similar analysis by Jommi & Galeone (2023) found that higher added therapeutic value and quality of clinical evidence were associated with receiving innovative status and full compared with conditional innovativeness, whereas therapeutic need was not a predictor of innovative status (63). They also found that a conditional innovativeness status was more likely for medicines for rare diseases. This indicates that the assessment system is rather transparent and consistent (63).

The innovative status is valid for 36 months (38). Furthermore, a full innovative status exempts the pharmaceutical company from paying any mandatory discount for its product to the state (also referred to as clawback payments) (58). In addition, only the first-to-market drug for a therapeutic indication can get the status for the full period of 36 months, whereas other followers for the same indication can only recoup the remaining time period of having the innovative status (64). If a drug is labeled as conditional innovative, it will be granted immediate access to the regional formularies but without reimbursement from the Fund and the exclusion from the clawback payment by the company. If more evidence becomes available for a conditional innovative drug, the company can apply again for a full innovative status after 18 months, which, if approved, will be granted for the remaining time of up to 36 months.

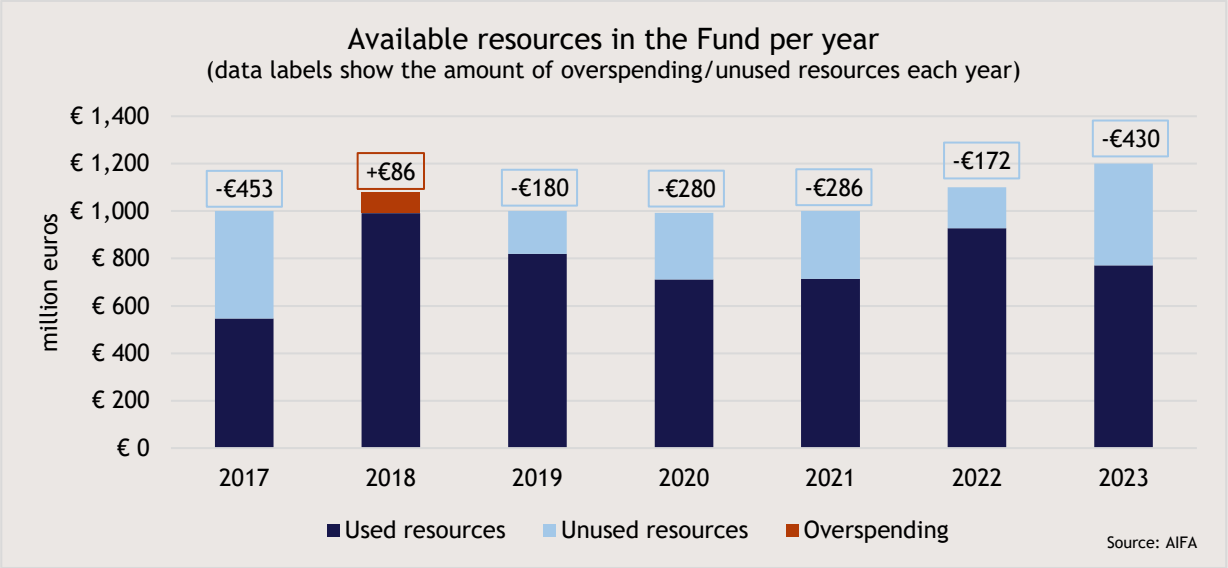
In 2023, a total of 43 assessments of innovativeness were made by AIFA of which 11 were granted full innovative status, 19 received conditional innovative status, and 13 had a negative decision (65). The total number of assessments was similar as in 2022, but considerably higher than in 2021 with 22 assessments. In general, most drugs that are assessed for innovative status are oncology drugs (60% of all decisions between 2017 and 2021) (58). According to Dr. Perrone, the relatively high number of innovative statuses granted could possibly affect the overall reimbursement rate and time in the country, as observed in the high ranking of Italy in the EFPIA WAIT indicator survey.



Unused resources in the Fund

Since its establishment in 2017, the Fund has been characterized by an underuse of resources compared to its total allocated budget. Apart from 2018, data from AIFA show that a considerable proportion of resources – around 15-35% - remain unused in the Fund every year (16). In 2023, the amount of spent resources was around €770 million (20), resulting in a gap of €430 million of unused resources (total budget of €1.2 billion). Whenever there are unused resources in a certain year, these earmarked financial resources by the Ministry of Economy remain simply unspent.

If the Fund exceeds its limit (as in 2018), the surplus would be paid back 50% by the pharmaceutical companies holding the patents for innovative drugs (according to their market share) and 50% by the regions to the Ministry of Economy. Overspending can have negative repercussions at the regional/hospital level. For instance, a law in the region of Puglia stipulates that the General Director of the local health unit will be dismissed if the spending limits for pharmaceutical expenditure are not respected (66). This might create an incentive for general directors to instruct physicians not to prescribe drugs (especially towards the end of the budget year) that cannot be fully covered with available resources from reimbursement funds.



According to Dr. Perrone, it is unfortunate that unused resources in the Fund exist, given that the overall financial resources allocated to the SSN and the regions are not adequate. The persistent existence of unused resources reflects (i) the lack of flexibility in the use and balance of available resources dedicated to the SSN, and (ii) a silo philosophy within the healthcare system that does not allow resources to be transferred across different pathways and departments. It is the view of Dr. Perrone that these unused resources should be used to improve the efficiency of the overall HTA system. According to Ms. Mancuso, the large and persistent proportion of unused resources in the Fund is due to the fact that some regions do not take advantage of the great opportunity provided by the Fund. Moreover, some clinicians are not informed about innovative drugs and therefore continue to administer traditional medicines. It is no coincidence that the majority of the resources made available by the Fund are utilized by hospitals that can rely on Cancer Centers of Excellence, as noted by Ms. Mancuso.

International comparison

In Europe, there are examples of countries that have adopted similar funding mechanisms for new innovative medicines. The table below summarizes such initiatives (also including funds for rare diseases). The Cancer Drugs Fund and the Innovative Medicines Fund in England are probably the closest examples to the Fund in Italy. According to Dr. Perrone, countries can have different reasons for establishing a dedicated fund for innovative medicines in the first place. For example, the Cancer Drugs Fund in England originated from a need to circumvent the otherwise strict criteria imposed by the HTA agency (NICE), whereas the purpose of the Fund in Italy was initially to provide a funding solution for oncology drugs that regions could not afford. According to Mr. Monti, there is no similar-sized fund in other European countries.

Overall, the existence of funds in various countries indicates that these countries see a value in having separate dedicated funds for innovative drugs and that how these funds are integrated in the overall HTA system is dependent on the local context and needs. Nevertheless, judging from the information provided in the table below, the Fund in Italy seems to have the most sophisticated system of payment processes, criteria and incentives.

Examples of innovative drug funds in European countries

Country	Description
Belgium	A "Special Solidarity Fund" exists from which patients can request funding from designated orphan drugs or treatments for rare diseases that meet specific criteria and which are not yet reimbursed by the compulsory health insurance. Reimbursement will only be granted if the patient has exhausted all other reimbursed treatment options (67).
Croatia	High-cost medicines can be financed from the "Especially Expensive Medicine Fund". This fund is separate from the Croatian Health Insurance Fund and costs for these medicines do not affect hospital budgets (25, 68).
England (UK)	The Cancer Drugs Fund (CDF) was established in 2010 and has been continuously revised and updated over the years (69). Its original purpose was to fund cancer medicines that the National Health Services (NHS) England would normally not fund after HTA appraisal. It was later changed to support managed access processes for a maximum period of two years to allow for additional follow-up data to be collected. According to the NHS England (69), the CDF delivers the following benefits: • Earlier access for patients to the most promising new treatments. • A fast-track HTA process for companies to apply for appraisals. • Clearer and faster decision-making about which cancer drugs are available. • All new cancer drugs and significant new licensed indications for cancer drugs are referred for appraisal. • Financial certainty with a fixed budget and a mechanism to control expenditure. • Patient access while uncertainty about a drug's effectiveness can be assessed through data collection. • Greater flexibility for NHS England in the deals agreed with the pharmaceutical industry to encourage the responsible pricing of cancer drugs. In 2021, an additional fund called "Innovative Medicines Fund" was established which aims to ensure funding for potentially life-saving treatments outside oncology (25). It functions alongside the CDF and on similar terms (70).
Poland	A "rescue access program" exists, which is a system for issuing approval for non-reimbursed treatments for patients for whom all publicly funded therapeutic options have been exhausted (71). Reimbursement by the National Health Fund can apply if its appropriateness has been confirmed. Another public funding mechanism for drugs with high clinical innovation exists as part of the Medical Fund (71).

Key benefits of the Fund

There are numerous benefits of the Funds for Innovative Drugs in Italy both from a patient perspective, the overall the HTA system, the SSN, and for companies that are developing and launching new treatments in Italy. The key benefits are described below.

✓ Timely patient access to innovative treatments

The Fund improves access to novel treatments for patients in Italy both from an availability and an affordability perspective. According to all experts (Dr. Perrone, Mr. Monti, Ms. Mancuso), the most important benefit of the Fund is the possibility to improve timely access for patients to new medicines. Dr. Perrone holds that the regional HTA procedures that exist today are redundant as there is already a well-established HTA system on the national level. By fast-tracking innovative treatments to the regional formularies, it allows for innovative drugs reach patients faster with a secure funding.

✓ More equal access across all regions

The national process for innovative medicines promotes the introduction in a more equal manner across the country, as noted by all experts (Dr. Perrone, Mr. Monti, Ms. Mancuso). In fact, regional inequalities are a problem in Italy, as emphasized in the National Oncology Plan 2023-2027 (22). Since a fully or conditional innovative drug is immediately placed on the regional formularies across the country, it improves the opportunity for patients to have equal access to these new medicines across all regions. According to Ms. Mancuso, the goal of reducing regional inequalities in access to cancer treatments has not been completely achieved, primarily due to the slow bureaucracy of the regions and the lack of awareness among some clinicians, who are unaware that they can rely on new innovative therapeutic treatments. As a result, regional inequalities, although reduced, continue to persist.

✓ Reduction of medicine spending in regional healthcare budgets

Each year, healthcare spending accounts for around 80% of the total regional budgets in Italy, which indicates that most regions have limited budget flexibility when it comes to spending on health care (72, 73). The establishment of the Fund has made the SSN and the regional healthcare systems more sustainable, as it removes the burden for the purchase of medicines that are known to be expensive for the regions. In addition, regions have different budget structures which makes it difficult to track spending on innovative treatments on a national level. The Fund has been proven to be a mechanism to control spending at the regional level (59). As noted by Dr. Perrone and Ms. Mancuso, the reduction in spending at the regional level due to the Fund is highly significant.

✓ Increased transparency and consistency of funding for innovative treatments and the overall HTA process

A fundamental principle for HTA is consistency and transparency (74, 75). A recent study among HTA agencies in 14 countries investigated features that could possibly affect access to medicines of which increased transparency of the HTA process was the main reason (76). A report by AIFA maintained that the multidimensional approach chosen by AIFA in 2017 (to establish the Fund and assessment of innovation alongside the conventional HTA process) indeed has reached the intended purpose both in terms of increasing transparency and accountability of the decision-making process applied to innovative medicines (58). Furthermore, AIFA notes that the use of the GRADE criteria for innovativeness could support the early identification of discrepancies between the available clinical evidence at the time of market approval and the need of patients to have rapid access to such innovative therapies (58).[4]

✓ Clear focus on the therapeutic value of new treatments

According to Ms. Mancuso, the focus on the therapeutic value of new treatments is a key benefit. Providing patients with adequate, innovative, and personalized care helps avoid wasting resources on inefficient or inadequate treatments, which could lead to disease progression and, consequently, higher costs for the SSN. This is where the therapeutic value becomes highly significant, both in terms of improving patient survival and generating savings for the healthcare system.

✓ Incentives for pharmaceutical companies to focus on innovation

The criteria imposed by the Fund to achieve an innovative status and the reward offered for fully innovative drugs – direct access to regional formularies and full reimbursement without mandatory discounts to the state for 36 months – provide strong financial incentives to companies (25). The criteria entice companies to focus on those qualities that AIFA uses to categorize innovation - unmet need, added therapeutic value, and quality of evidence.

✓ Stimulate research by making Italy attractive for investment in research activity

According to Mr. Monti, the Fund stimulates research. It helps to keep Italy at the global frontier of treatment standards and makes Italy attractive for investment in research activity.

[4] In relation to the HTA system in Italy in general, Mr. Monti noted that it would be beneficial to consider moving towards a horizontal approach with a more integrated approach in Italy. This approach should apply a societal perspective in HTA rather than focus only on the healthcare system. Costs for effective medicines might be recouped elsewhere outside the healthcare system, such as costs for sick leave, for social care, and for long-term care. By investing in medicines and accepting increasing medicine expenditure, the hope is to realize savings in the future as people become healthy and return to work and need less follow-up care.

Recommendations by the authors of this report

Given the numerous benefits of the Fund in Italy, it is critical that policymakers preserve the Fund as an integral part of the overall healthcare system. Regular evaluations of the performance of the Fund should be conducted to identify opportunities for improvements and secure sufficient budget allocations in the future. The main recommendation that the authors of this report put forward is to: "*Consider including drug indications with conditional innovative status in the Fund on similar terms as those with full innovative status, and use parts of the annual unused resources to finance drug indications with conditional innovative status.*"

As described above, if a drug is found to be conditional innovative, it will be granted immediate access to the regional formularies but without reimbursement from the Fund. If more evidence becomes available for a conditional innovative drug, the company can reapply for a full innovative status after 18 months, which, if approved, will be granted for the remaining time of up to 36 months. The number of drugs with conditional innovative status varies from year to year. As shown above, in 2021 there was no drug indication with conditional innovative status, whereas in 2022 there were four such indications and in 2023 there were 19 indications.

An advantage of starting to reimburse drugs with conditional innovative status from the Fund is that a larger number of patients could gain access to products deemed innovative and, consequently, to cutting-edge treatments and therapies that would otherwise be out of reach, as noted by Ms. Mancuso. It is crucial, however, that — as always, given that we are dealing with newly approved drugs — patients receiving these treatments are closely monitored in order to record their benefits and any side effects. The patient experience must be carefully documented and registered to optimize treatment pathways and facilitate the broader distribution and administration of the new drug to other patients, according to Ms. Mancuso.

In order to maintain a distinction between drugs with full innovative status and conditional innovative status, the duration of the funding could be different. Drugs with full innovation status should retain the duration of 36 months, while medicines with conditional innovation status could receive a shorter duration of, for example, 18 months. The company of the drug with conditional innovative status should be able to reapply for full innovation status after 18 months, which, if approved, would grant continued funding for the remaining duration of up to 36 months. Such a distinction in the duration of funding could help manage the additional costs of including medicines with conditional innovative status, without running a major risk that the Fund starts to overspend.

Another recommendation by the authors of this report is to: "*Preserve incentives for pharmaceutical companies to focus on innovative areas of application throughout the entire life cycle of their products.*" Upon initial marketing authorization, the full extent of the effectiveness of a medicine in all possible clinical settings is usually not known. Indeed, clinical research to explore new areas of application and conduct clinical trials is time-consuming and takes many years. To uphold the incentives to conduct research beyond initial marketing authorization and over the entire product lifecycle is therefore critical for versatile medicines.

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Appendix: AIFA criteria for innovation status

Criteria	Levels of ranking				
1. Therapeutic need	**Maximum** (no alternative therapeutic options available)	**Important** (alternative therapeutic options available, with no impact on clinically relevant outcomes)	**Moderate** (alternative therapeutic options available with limited impact on clinically relevant outcomes, and/or uncertain or not satisfactory safety profile)	**Poor** (alternative therapeutic options available with high impact on clinically relevant outcomes and a satisfactory safety profile)	**Absent** (alternative therapeutic options available, which are able to slow down the progression of the disease and have a satisfactory safety profile)
2. Added therapeutic value	**Maximum** (greater efficacy than alternative therapeutic options (if available) in clinically relevant outcomes, ideally curing the disease or altering its natural history)	**Important** (greater efficacy based on clinically relevant outcomes, or alternatively one of the following options: i) the drug can reduce the risk of seriously debilitating or life-threatening complications, ii) the drug has a better risk/benefit ratio compared to the alternative therapeutic options, iii) the drug can avoid the use of high-risk clinical procedures, iv) the drug can significantly change the natural history of the disease in a subpopulation of patients, v) the drug can provide a clinically relevant added value, e.g., in terms of quality of life and disease-free interval, compared to the available therapeutic options)	**Moderate** (a slightly better efficacy profile or improved efficacy in some patient subpopulations or based on surrogate endpoints and has limited impact on the quality of life. For situations where the lack of a study comparator is acceptable, evidence showing relative efficacy compared to the available therapeutic options should be taken into account)	**Poor** (greater efficacy only for non-clinically relevant outcomes or based on a poor magnitude of effect. The drug offers minor benefits (e.g., favorable routes of administration) compared to the available therapeutic options)	**Absent** (no added therapeutic benefit compared to the alternative available therapeutic options)
3. Quality of clinical evidence	**High**	**Moderate**	**Low**	**Very low**	

Source: Fortinguerra et al. (2021) (58).


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