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KEY DRIVERS OF INNOVATIVENESS APPRAISAL FOR MEDICINES: A CRITICAL REVIEW OF THE ITALIAN EXPERIENCE AFTER THE ADOPTION OF THE NEW RANKING SYSTEM

Running title: Innovativeness appraisal for medicines in Italy

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ABSTRACT

Objective: In 2017, the Italian Medicines Agency (AIFA) introduced a standardized process to appraise innovativeness of medicines. Innovative medicines are provided speeder market access and dedicated funds. Innovativeness criteria are: unmet therapeutic need, added therapeutic value and quality of the evidence (GRADE method). We investigated the role played by these three criteria on the final decision, if these criteria have been consistently used over time and if other variables have influenced decision-making.

Design: Critical review and data analyses of appraisal reports on innovativeness. No patients were directly involved in this study.

Setting and Participants: We scrutinized 54 appraisals reports available on AIFA's website (2017-2019).

Primary and secondary outcome measures: The impact of the three domains on final decision was investigated through a contingency table with Chi-square or Fisher's exact test, as appropriate. The consistency of the process over time was investigated through a recursive algorithm for innovativeness, using a deterministic approach.

Results: Among 54 appraisal reports on innovativeness available, 35 (65%) and 19 (35%) were for oncology and non-oncology medicines, respectively. The appraisals were equally distributed among "fully innovative" (35%), "conditionally innovative" (32%) and "not innovative" (33%). Added therapeutic value was the most important driver on innovativeness decision, followed by quality of the evidence. More recently appraised medicines, orphan designation, pediatric/mixed indications, and medicines approved with at least one supportive RCT were appraised 'innovative' by a larger proportion, but no statistical significance was found. The recursive algorithm shows a high level of internal consistency, accounting for 81% of appraisals.

Conclusions: Despite some limitations, including the moderate number of appraisals, this paper provides an insight into the determinants of innovativeness appraisals for medicines in Italy and the consistency of the appraisal process. This has important implications in terms of transparency and accountability in the prioritization process applied to innovative medicines.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- After the introduction in Italy of a new process for appraising medicines innovativeness in 2017, the drivers of innovativeness appraisal of medicines and the consistency of the relevant appraisal process were here investigated for the first time.

- The results of this study have important implications in terms of transparency and accountability in the prioritization process applied to innovative medicines.

- This study was based on a limited number of appraisals, but we systematically considered all the available ones.

INTRODUCTION

Market Access for pharmaceuticals in Italy is managed by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA). AIFA, differently from most other European Countries medicines agencies, have both regulatory and access competences[1]. The latter include the negotiation of reimbursement, ex-factory price and managed entry agreements and the appraisal of innovativeness status, possibly required by the pharmaceutical companies at market launch or autonomously carried out by AIFA[2]. Innovativeness status has some advantages from an access perspective, including two dedicated funds (one for cancer medicines and the other for non-cancer medicines) and immediate access to regional markets.

The criteria to get innovativeness status, which can be attributed only to drugs indicated for serious illnesses (*life-threatening diseases; diseases producing frequent hospitalizations or causing disabilities that can seriously compromise quality of life*") are the unmet therapeutic need, the added therapeutic value and the quality of the evidence (Determina AIFA 519/2017)[3].

The **unmet therapeutic need** is rated as:

- *Maximum*: there are no alternatives for that specific indication;
- *Important*: there are a few alternatives, but with no impact on clinically relevant endpoints;
- *Moderate*: there are alternatives with a limited and/or uncertain or unreliable impact on clinically relevant endpoints;
- *Poor:* there are alternatives for the same indication with clinically proven reliable results;
- *Absent*: there are alternatives for the same indication with an important impact on the natural history of the disease.

The added **therapeutic value**, that refers to clinical benefit, can be rated as:

- *Maximum*: the new drug has proven larger efficacy than any possible existing alternatives. In this case, the treatment is able to either cure the illness or significantly alter its natural history;
- *Important*: the new drug has a proven larger efficacy measured on clinically relevant endpoints, decreases the risk of invalidating or fatal complications, avoids highly dangerous clinical procedures or has more favorable risk/benefit (R/B) ratio than any available alternatives. In a subset of patients, the treatment either modifies the natural history of the disease or is beneficial in other clinically significant ways, e.g. in terms of quality of life or disease-free intervals, when compared to available alternatives;
- *Moderate*: the new drug has a larger efficacy than any available alternatives, but it is only moderate or only proven in some subsets of patients, with limited impact on the quality of life;
- *Poor*: the new drug has either a limited improvement of efficacy or has been proven on endpoints which are not clinically relevant. Minor advantages, e.g. more acceptable administration route;
- Absent: the new drug has no relevant benefit when compared to other available treatments.

Endpoints relevance has been specified for cancer medicines, being overall survival (OS) considered the gold standard, and the lack of OS data needed to justify. The document quotes that progression-free survival (PFS), disease-free survival (DFS), full response time or other surrogated endpoints (with already established clinical benefits) may be taken into account, according to indication and settings. Toxicity is also considered to evaluate the treatment's adequacy.

To appraise the **quality of evidence**, AIFA has chosen the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method[4]. According to this approach, the quality of clinical evidence can be graded as high, moderate, low or very low. The choice of GRADE methodology was aimed at improving the transparency and reproducibility of the appraisal process; this structured and flexible methodological tool provides a systematic approach in the assessment and is meant to minimize biases and improve consistency of the decisions[5].

The innovativeness is appraised per indication, and the innovativeness status lasts three years. The appraisal model represents a common framework for all indications, even if safeguard clauses are provided for rare indications where the quality of the evidence is more likely to be lower.

The industry usually applies for innovativeness, even if AIFA can proceed to evaluate it regardless of the industry' application. The innovativeness request is appraised by the AIFA's Technical-Scientific Committee (CTS). CTS may decide for full innovativeness, conditional innovativeness or non-innovative. Conditionally innovative medicines share with fully innovative medicines only the immediate access to regional markets. Conditional innovativeness is granted when the evidence is not sufficiently mature to provide a full innovativeness status and lasts 18 months.

Innovativeness may be granted, if both unmet need and added therapeutic value are graded "Maximum" or "Important" and the quality of evidence is rated "High". Conversely, if the unmet need or the added therapeutic value are graded "Poor" or "Absent", or the quality of evidence is rated "Low" or "Very Low" innovativeness will be not granted. For rare indications the

innovative status may be granted even if the quality of evidence is graded "Low", but the unmet need and the added therapeutic value are both at least "Important" (Figure 1).

Pharmaceutical companies are informed by AIFA on the intended final appraisal and can rebut on appraisals in ten days. The final appraisal is published on the AIFA's website, together with a short description of the rationale behind the decision taken (www.aifa.gov.it).

Despite the growing interest in this new criteria and the relevant appraisal process[6], there is no evidence on the role played by the three criteria on the final decision, if these criteria have been consistently used overtime and if other variables do influence the innovativeness status.

METHODS

Appraisal reports on innovativeness were downloaded from the AIFA's website[7] as at 31 December 2019: 54 appraisal reports were found, 35 and 19 for oncology and non-oncology medicines respectively.

The following data were retrieved from the appraisal reports and inserted into an extraction template:

- final appraisal ("fully innovative", "conditionally innovative" or "not innovative");
- rank attributed to the unmet need, the added therapeutic value and the quality of evidence;
- variables that may have an influence on the final decision taken by the CTS, including:
  - the target disease: oncological (solid/hematological) disease or non-oncological disease (infectious/autoimmune/other diseases);
  - population: adult, pediatric, mixed;
  - orphan drug designation by EMA (European Medicines Agency): yes or no;
  - number of "Summaries of Findings" (SoF) according to the GRADE system that reported the key information concerning the magnitudes of relative and absolute effects of the interventions examined, the amount of available evidence and the certainty (or quality) of available evidence[8];
  - number of clinical studies considered;
  - number of randomized clinical trials (RCT), supporting the application for innovativeness;
  - number of observational studies, supporting the application for innovativeness;
- appraisal date.

We firstly calculated some descriptive statistics: frequencies and percentages for categorical variables; mean and median values, standard deviations (SD), quartiles and extreme values for continuous variables.

Afterwards, we scrutinized the role played by the above-mentioned variables on the innovativeness appraisal. Fully innovative and conditionally innovative appraisals were merged, given the limited number of appraisal reports. Categorical data were analyzed using a contingency table with the Chi-square or Fisher's exact test, as appropriate. Continuous data were analyzed using a Student's T-test, after checking for normal distribution (based on the Shapiro-Wilk statistic), or a Wilcoxon rank-sum test otherwise.

Finally, we developed a recursive algorithm for innovativeness, using a determinist approach, to scrutinize the role played by the three above-mentioned criteria (unmet need, therapeutic added value, quality of the evidence).

Patient and Public Involvement

No patients were directly involved in this study.

RESULTS

Figure 2 shows that appraisals were equally distributed among "fully innovative" (35% of the total), "conditionally innovative" (32%) and "not innovative" (33%).

Cancer medicines were more often appraised as potentially innovative, whereas other drugs show a higher proportion of non-innovative status (29% cancer drugs were appraised not innovative, compared to 42% non-cancer treatments), but the difference was not significant (p=0.42).

The role played on innovativeness status by the appraisal year, orphan designation, target disease, target population, number of Summary of Findings, overall number of studies, number of RCT and Phase I/II studies are illustrated in Table 1.

Table 1. Variables detected on the appraisal document and innovativeness status (2017-2019).

	ALL DISEASES (n=53 [a])				ONCOLOGY (n=34 [a])				NON-ONCOLOGY (n=19)			
	All medicines	*Innovative[b]*	*Not innovative*	*p-value*	*All medicines*	*Innovative[b]*	*Not Innovative*	*p-value*	*All medicines*	*Innovative[b]*	*Not Innovative*	*p-value*
CTS appraisal year	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	
2017	27 (50.9)	17 (63.0)	10 (37.0)		17 (50.0)	11 (64.7)	6 (35.3)		10 (52.6)	6 (60.0)	4 (40.0)	
2018	21 (39.6)	14 (66.7)	7 (33.3)		13 (38.2)	9 (69.2)	4 (30.8)		8 (42.1)	5 (62.5)	3 (37.5)	
2019	5 (9.4)	4 (80.0)	1 (20.0)	0.76	4 (11.8)	4 (100.0)	0 (0.0)	0.38	1 (5.3)	0 (0.0)	1 (100.0)	0.48
Orphan designation												
No	18 (33.9)	10 (55.5)	8 (44.5)		11 (32.3)	8 (72.7)	3 (27.3)		8 (42.1)	3 (37.5)	5 (62.5)	
Yes	35 (66.1)	25 (71.4)	10 (28.6)	0.25	23 (67.7)	16 (69.6)	7 (30.4)	0.98	11 (57.9)	8 (72.7)	3 (27.3)	0.18
Disease												
Solid tumours	19 (35.8)	14 (73.7)	5 (26.3)		19 (55.9)	14 (73.7)	5 (26.3)		-	-	-	
Hematological malignancies	15 (28.3)	10 (66.7)	5 (33.3)		15 (44.1)	10 (66.7)	5 (33.3)	0.97	-	-	-	
Infectious diseases	5 (9.4)	3 (60.0)	2 (40.0)		-	-	-		5 (26.3)	3 (60.0)	2 (40.0)	
Autoimmune diseases	2 (3.8)	0 (0)	2 (100.0)		-	-	-		2 (10.5)	0 (0.0)	2 (100.0)	

Other	12 (22.7)	8 (66.7)	4 (33.3)	0.33	-	-	-		12 (63.2)	8 (66.7)	4 (33.3)	0.21
Population												
Adults only	45 (84.9)	29 (64.4)	16 (35.6)		31 (91.2)	22 (71.0)	9 (29.0)		14 (73.7)	7 (50.0)	7 (50.0)	
Pediatric or mixed	8 (15.1)	6 (75.0)	2 (25.0)	0.70	3 (8.8)	2 (66.7)	1 (33.3)	0.99	5 (26.3)	4 (80.0)	1 (20.0)	0.34
Mean number SoF (SD)	3.6 (3.3)	3.4 (2.9)	4.1 (4.0)	0.88	2.7 (2.5)	2.8 (2.6)	2.6 (2.5)	0.43	5.3 (3.9)	4.8 (3.2)	5.9 (4.9)	0.80
N studies												
1	41 (77.4)	27 (65.8)	14 (34.1)		31 (91.2)	21 (67.7)	10 (32.3)		10 (52.6)	6 (60.0)	4 (40.0)	
>1	12 (22.6)	8 (66.7)	4 (33.3)	0.99	3 (8.8)	3 (100.0)	0 (0.0)	0.54	9 (47.4)	5 (55.6)	4 (44.4)	0.99
N RCT												
0	12 (22.6)	7 (58.3)	5 (41.7)		11 (32.3)	6 (54.5)	5 (45.5)		1 (5.3)	1 (100.0)	0 (0.0)	
1	31 (58.5)	22 (71.0)	9 (29.0)		21 (61.8)	16 (76.2)	5 (23.8)		10 (52.6)	6 (60.0)	4 (40.0)	
>1	10 (18.9)	6 (60.0)	4 (40.0)	0.66	2 (5.9)	2 (100.0)	0 (0.0)	0.28	8 (42.1)	4 (50.0)	4 (50.0)	0.62
N clinical trials phase I/II												
0	39 (73.6)	26 (66.7)	13 (33.3)		23 (67.6)	18 (78.3)	5 (21.7)		16 (84.2)	8 (50.0)	8 (50.0)	
≥1	14 (26.4)	9 (64.3)	5 (35.7)	0.99	11 (32.4)	6 (54.5)	5 (45.5)	0.23	3 (15.8)	3 (100.0)	0 (0.0)	0.23

[a] For one cancer drug (daratumumab) one appraisal was duplicated (innovativeness status was confirmed). For this reason, only one evaluation was considered in the present analysis.

[b] Innovative status includes fully and conditionally innovative.

CTS: Technical-scientific committee; SoF: Summaries of Findings; RCT: Randomized Clinical Trial.

More recently assessed medicines, orphan drugs, pediatric/mixed indications, and medicines approved with at least one RCT were appraised innovative by a larger proportion. However, none of these variables has a significant impact from a statistical viewpoint. In oncological setting, innovative drugs provided on average more RCT evidence in support of the application when compared to non-oncological ones. Furthermore, rarity (according to the orphan drug definition), and type of disease did not seem to be determinant for the innovativeness evaluation. Similarly, in the non-oncological setting, no significant differences were found in basic properties between innovative and not innovative indications. Non-oncological forms have a higher number of RCT supporting them compared to oncological ones (more than 1 RCT supporting 42% of non-oncological ones compared to approximately 6% of oncological ones). As a second step, we investigated the role of each of the three domains on appraisals. Table 2 shows the association between unmet therapeutic need, added therapeutic need and quality of evidence and the final appraisal.

Table 2. Role played by the three domains on innovativeness status (2017-2019).

	All medicines	*Innovative*	*Not innovative*	*p-value*
Unmet therapeutic need				
N [a]	53	35	18	
Maximum (Scale=1)	8 (15.1%)	5 (62.5%)	3 (37.5%)	
Important (Scale=2)	23 (43.4%)	16 (69.6%)	7 (30.4%)	
Moderate (Scale=3)	19 (35.8%)	14 (73.7%)	5 (26.3%)	
Poor (Scale=4)	3 (5.7%)	0 (0.0%)	3 (100.0%)	0.09
Range	1 - 4	1 - 3	1 - 4	
Mean (SD)	2.3 (0.8)	2.3 (0.7)	2.4 (1.0)	0.57
Median (Range IQ)	2 (2-3)	2 (2-3)	2 (2-3)	
Added therapeutic value				
N [a]	52 [b]	35	17 [b]	
Maximum (Scale=1)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Important (Scale=2)	18 (34.6%)	16 (88.9%)	2 (11.1%)	
Moderate (Scale=3)	22 (42.3%)	19 (86.4%)	3 (13.6%)	
Poor (Scale=4)	12 (23.1%)	0 (0.0%)	12 (100.0%)	<0.01
Range	2 - 4	2 - 3	2 - 4	

Mean (SD)	2.9	(0.8)	2.5	(0.5)	3.6 (0.7)	<0.01
Median (Range IQ)	3	(2-3)	3	(2-3)	4 (3-4)	
Quality of clinical evidence						
(GRADE evaluation)						
N [a]	53		35		18	
High (Scale=1)	7	(13.2%)	6	(85.7%)	1 (14.3%)	
Moderate (Scale=2)	26	(49.1%)	20	(76.9%)	6 (23.1%)	
Low (Scale=3)	16	(30.2%)	9	(56.2%)	7 (43.8%)	
Very low (Scale=4)	4	(7.5%)	0	(0.0%)	4 (100.0%)	0.01
Range	1 - 4		1 - 3		1 - 4	
Mean (SD)	2.3	(0.8)	2.1	(0.7)	2.8 (0.9)	<0.01
Median (Range IQ)	2	(2-3)	2	(2-3)	3 (2-3)	

IQ: interquartile; SD: standard deviation

[a] One evaluation was duplicate for innovativeness time extension (#12 and #42-Daratumumab). For this reason, only one evaluation was considered in the present analyses.

[b] For one rating (#10-Nivolumab), the added therapeutic value was reported as "not assessable".

A significant difference between innovative and not innovative outcomes was found both for the added therapeutic value and the quality of evidence domains ($p < 0.01$). For innovative and non-innovative indications, the added therapeutic value had an average score of 2.5 (between "Moderate" and "Important") and 3.6 (between "Poor" and "Moderate") respectively. The quality of evidence for innovative and non-innovative medicines had an average score of 2.1 ("Moderate"), and 2.8 (between "Low" and "Moderate") respectively.

The average scores of unmet need for innovative and not innovative evaluations were quite similar.

Taking into account the above-mentioned findings, we developed a decision tree using a deterministic approach (Figure 3).

The flowchart illustrated by Figure 3 confirms that added therapeutic value was the most influential parameter, followed by GRADE evaluation, whereas the unmet therapeutic need had a quite limited impact on the final appraisal. When the added therapeutic value was rated as "poor" or "absent", or when the GRADE evaluation was "very low", the indication is never considered innovative. Innovativeness resulted from an at least a "moderate" added therapeutic value combined with an at least a "moderate" GRADE evaluation.

The decision tree accounted for 43 out of 53 cases (81%). As for the other 10 appraisals, six of them were either "conditionally innovative" or "not innovative" because they had "moderate" added therapeutic value and a "low" GRADE evaluation. The other four cases were given either a "full" or a "conditioned" innovativeness because they had a "moderate" added therapeutic value along with a "high" GRADE evaluation. When the final assessment was uncertain, it was not possible to discern factors determining the final appraisal, nor to find out the driver from the

characteristics of the indication, such as the disease (oncological or non-oncological) or the rarity of the disease.

DISCUSSION

The present study analyzed the new AIFA approach to appraise innovativeness for medicines. The appraisal process relies on three criteria: unmet therapeutic need, added therapeutic value, and quality of clinical evidence assessed with GRADE method. Despite the growing interest in this new appraisal process, there is still no evidence on the role played by the three criteria on the final decision, if these criteria have been consistently used overtime and if other variables do influence the innovativeness status. We found that added therapeutic value was the most influential parameter, followed by quality of evidence, whereas unmet therapeutic need had a quite limited impact on the final appraisal. It seems that a high unmet therapeutic need is perceived as a prerequisite of innovativeness, instead of being the driver of the appraisal process. We investigated the potential role of other variables – namely the characteristics of the drugs and the evidence provided – that is whether there is a systematic correlation between these variables and innovativeness status. Some relationships were found: for examples, a larger proportion of orphan drugs were appraised innovative. However, the statistical significance of these relationships is law. We have also investigated the consistency of the appraisal process. Despite the high level of discretion left to the Scientific Committee in appraising the unmet need and the added therapeutic value, this process looked intrinsically coherent.

Other countries have relied on a formal appraisal of added therapeutic value. This is done for example in France and Germany where all new drugs and indications are appraised and added therapeutic value is ranked in five and six levels respectively[1]. Ranks are used for price / discount negotiations. In France the absolute benefit is ranked too and used to take decisions on reimbursement (introduction in the positive list and co-payment). There is evidence on the (i) coherence between ranks attributed in the two countries to the same medicine[9], consistency

between these rankings and other way of measuring added value by HTA organisations (e.g. between the added therapeutic value rank in France and QALYs – Quality Adjusted Life Years gained - in England[10]) and scientific societies[11] and the role played by the added therapeutic value in price/discount negotiation[12]. Italy is the only country in Europe where (i) innovativeness status is appraised on the grounds of a ranked unmet need, added therapeutic value and quality of the evidence, (ii) innovative medicines are provided a speeder market access and dedicated funds and (iii) added therapeutic value rank is not used in price negotiation. As a consequence, our results, besides being the first one published on the Italian-case, cannot be fully compared with that of our countries.

The study has some limitations. Firstly, it is based on a quite small number of appraisals (n = 54). As already mentioned, innovativeness appraisals can be requested by the companies or spontaneously carried out by AIFA. The information on the applicant was not available and no stratified analysis could be performed, despite it would have been very interesting. We could analyze only the final appraisal published by AIFA, but we did not have any access to the applications submitted by the companies. This implies that the results of the present study cannot be considered a predictor of the response by AIFA to the applicant. However, our analysis was aimed at evaluation of the key drivers and the consistency of the AIFA decision-making process, rather than the comparison of applications submitted by the companies and final decision of AIFA.

CONCLUSIONS

Despite the above-mentioned limitations, our analysis has some important implications. Companies are pushed to provide solutions with an added therapeutic value and a high quality of evidence, since the latter are the driver of innovativeness, which brings important advantages for market access. We are aware that investments by the pharmaceutical companies are taken globally, but the more HTA agencies insist on clear and transparent criteria to appraise new medicines, the higher will be the impact on the management of pipelines by the pharmaceutical companies.

The new process implemented by AIFA has also the advantage of enhancing transparency, accountability and, because of its intrinsic consistency, predictability of innovativeness appraisals, thus making access in Italy more reliable in this respect.

Last but not least, prioritization of access through innovativeness is managed transparently, on the grounds of quite objective criteria and providing the whole stakeholders with the rationale of decision taken.

The process could be further enhanced, for example including in a more structured framework patients reported outcome measures, whereas at present the appraisal process mostly relies on clinical variables, and proving for an interaction between innovativeness (and its domains) appraisals and price negotiation. Furthermore, future appraisals may confirm or disconfirm the pathway we have traced from the evidence collected.

However, the new innovativeness appraisal system can be considered an important step towards a more transparent and evidence-based management of access to medicines in Italy.

Contributors: CG, PB and CJ designed the study and developed the methods. CG and PB reviewed the literature. CG, PB and CJ contributed to the data analysis and interpretation. CG prepared the tables. CG and CJ drafted the manuscript. PB provided critical review of the manuscript. All authors have reviewed and approved the final version of the manuscript for publication.

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Data Statement: Data are available in a public, open access repository. Appraisal reports on innovativeness are publicly downloadable from the AIFA's website at https://www.aifa.gov.it/farmaci-innovativi.

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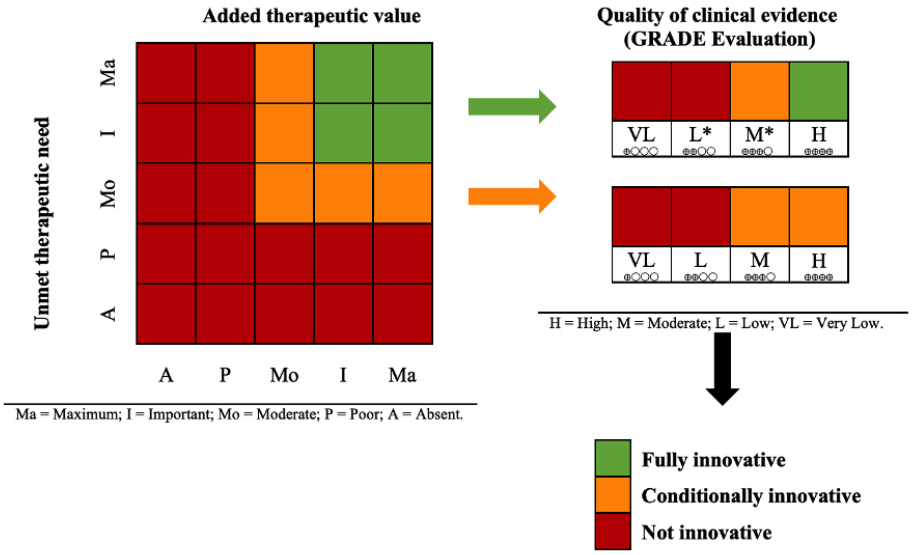

Figure 1. Criteria used to evaluate innovativeness adopted by Italian Medicines Agency.

Adapted from Recchia, 2017 13
* For rare disease there is the following exception: the fully innovative is attributed in the presence of at least important unmet therapeutic need and added therapeutic value in presence of at least low quality of clinical evidence.

170x108mm (144 x 144 DPI)

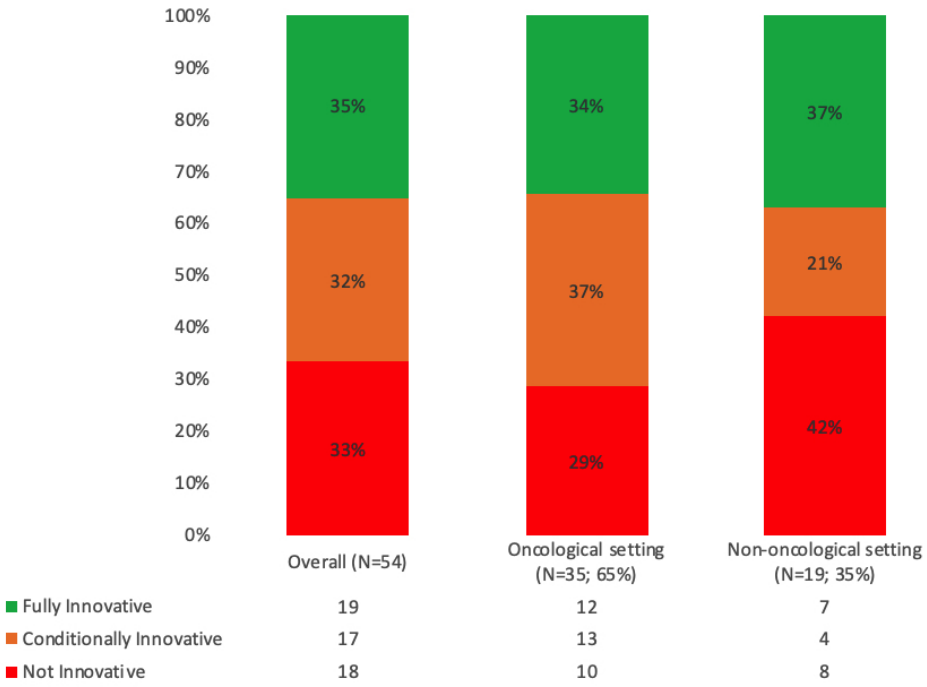

Figure 2. Innovative appraisals by the Italian Medicines Agency (2017-2019).

155x117mm (144 x 144 DPI)

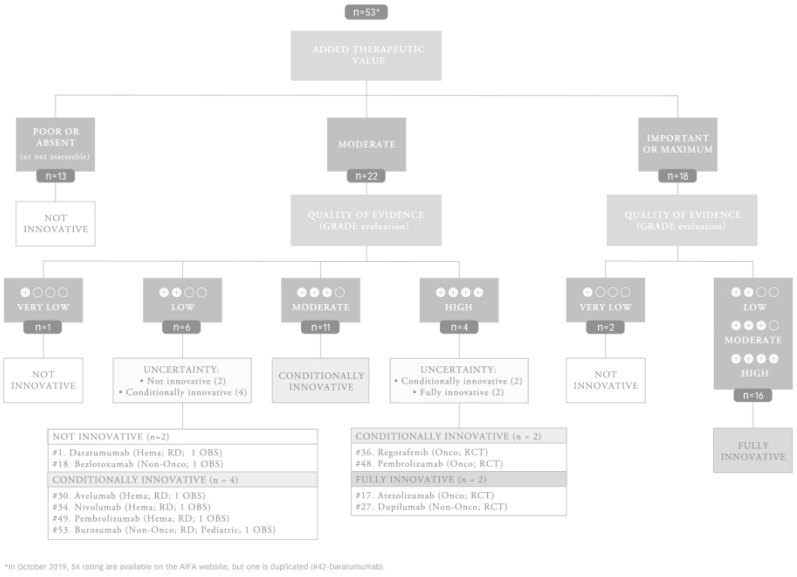

Figure 3. Deterministic decision tree based on the available appraisals (2017-2019).

#Nr. Indicate the drug innovativeness evaluation form available on the AIFA website
Onco: Oncology
Hema: Hematology
RD: rare disease
OBS: Observational study
RCT: Randomized Clinical Trial

217x130mm (300 x 300 DPI)

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KEY DRIVERS OF INNOVATIVENESS APPRAISAL FOR MEDICINES: THE ITALIAN EXPERIENCE AFTER THE ADOPTION OF THE NEW RANKING SYSTEM

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KEY DRIVERS OF INNOVATIVENESS APPRAISAL FOR MEDICINES: THE ITALIAN EXPERIENCE AFTER THE ADOPTION OF THE NEW RANKING SYSTEM

Running title: Innovativeness appraisal for medicines in Italy

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ABSTRACT

Objective: In 2017, the Italian Medicines Agency (AIFA) introduced a standardized process to appraise innovativeness of medicines. Innovative medicines are provided speeder market access and dedicated funds. Innovativeness criteria are: unmet therapeutic need, added therapeutic value and quality of the evidence (GRADE method). We investigated the role played by these three criteria on the final decision aimed to understand how the new Italian innovativeness appraisal framework was implemented.

Design: A desk research gathered AIFA's appraisals reports on innovativeness and data analyses were conducted. No patients were directly involved in this study.

Setting and Participants: We scrutinized all 77 appraisals reports available on AIFA's website (2017-2020).

Primary and secondary outcome measures: The impact of the three domains on final decision was investigated through a series of univariate analyses. A recursive algorithm for innovativeness using a determinist approach (merely data-driven) to scrutinize the role played by the three domains was performed.

Results: Among 77 appraisal reports on innovativeness available, 49 (64%) and 28 (36%) were for oncology and non-oncology medicines, respectively. The appraisals were equally distributed among "fully innovative" (36%), "conditionally innovative" (30%) and "not innovative" (34%). Added therapeutic value was the most important driver on innovativeness decision, followed by quality of the evidence. Drugs for rare diseases and with pediatric/mixed indications were appraised 'innovative' by a larger proportion, but no statistical significance was found. The recursive algorithm shows a good descriptive accuracy, accounting for 82% of appraisals.

Conclusions: Despite some limitations, including the moderate number of appraisals, this paper provides an insight into the determinants of innovativeness appraisals for medicines in Italy and the accuracy of the appraisal process. This has important implications in terms of transparency and accountability in the prioritization process applied to innovative medicines.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is an original, up to date analysis of the new National Drugs Agency appraisals framework for drug innovativeness in the Italian setting
- This study was based on a limited number of appraisals, but we systematically considered all the available ones
- The relatively small number of appraisals did not allow to analyze possible different patterns of association between the three innovativeness criteria and the type of innovativeness (i.e., fully or conditionally innovative)

INTRODUCTION

Market Access for pharmaceuticals in Italy is managed by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA). AIFA, differently from most other European Countries medicines agencies, have both regulatory and access competences.[1] The latter include the negotiation of reimbursement, ex-factory price and managed entry agreements and the appraisal of innovativeness status, possibly required by the pharmaceutical companies at market launch or autonomously carried out by AIFA.[2] Innovativeness status has some advantages from an access perspective, including two dedicated funds (one for cancer medicines and the other for non-cancer medicines) and immediate access to regional markets.

The criteria to get innovativeness status, which can be attributed only to drugs indicated for serious illnesses (*life-threatening diseases; diseases producing frequent hospitalizations or causing disabilities that can seriously compromise quality of life*") are the unmet therapeutic need, the added therapeutic value and the quality of the evidence (Determina AIFA 519/2017).[3]

The **unmet therapeutic need** is rated as:

- *Maximum*: there are no alternatives for that specific indication;
- *Important*: there are a few alternatives, but with no impact on clinically relevant endpoints;
- *Moderate*: there are alternatives with a limited and/or uncertain or unreliable impact on clinically relevant endpoints;
- *Poor:* there are alternatives for the same indication with clinically proven reliable results;
- *Absent*: there are alternatives for the same indication with an important impact on the natural history of the disease.

The added **therapeutic value**, that refers to clinical benefit, can be rated as:

- *Maximum*: the new drug has proven larger efficacy than any possible existing alternatives. In this case, the treatment is able to either cure the illness or significantly alter its natural history;
- *Important*: the new drug has a proven larger efficacy measured on clinically relevant endpoints, decreases the risk of invalidating or fatal complications, avoids highly dangerous clinical procedures or has more favorable risk/benefit (R/B) ratio than any available alternatives. In a subset of patients, the treatment either modifies the natural history of the disease or is beneficial in other clinically significant ways, e.g. in terms of quality of life or disease-free intervals, when compared to available alternatives;
- *Moderate*: the new drug has a larger efficacy than any available alternatives, but it is only moderate or only proven in some subsets of patients, with limited impact on the quality of life;
- *Poor*: the new drug has either a limited improvement of efficacy or has been proven on endpoints which are not clinically relevant. Minor advantages, e.g. more acceptable administration route;
- Absent: the new drug has no relevant benefit when compared to other available treatments.

Endpoints relevance has been specified for cancer medicines, being overall survival (OS) considered the gold standard, and the lack of OS data needed to justify. The document quotes that progression-free survival (PFS), disease-free survival (DFS), full response time or other surrogated endpoints (with already established clinical benefits) may be taken into account,

according to indication and settings. Toxicity is also considered to evaluate the treatment's adequacy.

To appraise the **quality of evidence**, AIFA has chosen the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.[4] According to this approach, the quality of clinical evidence can be graded as high, moderate, low or very low. The choice of GRADE methodology was aimed at improving the transparency and reproducibility of the appraisal process; this structured and flexible methodological tool provides a systematic approach in the assessment and is meant to minimize biases and improve consistency of the decisions.[5]

The innovativeness is appraised per indication, and the innovativeness status lasts three years. The appraisal model represents a common framework for all indications, even if safeguard clauses are provided for rare indications where the quality of the evidence is more likely to be lower.

The industry usually applies for innovativeness, even if AIFA can proceed to evaluate it regardless of the industry' application. The innovativeness request is appraised by the AIFA's Technical-Scientific Committee (CTS). CTS may decide for full innovativeness, conditional innovativeness or non-innovative. Conditionally innovative medicines share with fully innovative medicines only the immediate access to regional markets. Conditional innovativeness is granted when the evidence is not sufficiently mature to provide a full innovativeness status and lasts 18 months.

The new decision rule adopted by AIFA (Figure 1)[6] consists to grant innovativeness if both unmet need and added therapeutic value are graded "Maximum" or "Important" and the quality of evidence is rated "High" (green zone). Conversely, if the unmet need or the added therapeutic

value are graded “Poor” or “Absent”, or the quality of evidence is rated “Low” or “Very Low” innovativeness will be not granted (red zone). For rare indications, the innovative status may be granted even if the quality of evidence is graded “Low”, but the unmet need and the added therapeutic value are both at least “Important”. To note, in the intermediate situations (grey zone) there is uncertainty about innovation status, and AIFA decides case-by-case.

Pharmaceutical companies are informed by AIFA on the intended final appraisal and can rebut on appraisals in ten days. The final appraisal is published on the AIFA’s website, together with a short description of the rationale behind the decision taken (www.aifa.gov.it).

Despite the growing interest in this new criteria and the relevant appraisal process,[7] to our knowledge only preliminary descriptive analyses (based on less of 20 innovativeness appraisals updated to 2018) were available[8–10] and no clear and robust evidence emerged on the role played by the three criteria on the final decision, if these criteria have been consistently used over time and if other variables influence the innovativeness status.

Our analyses, based on available innovativeness appraisals updated to July 2020, aim to cover these information gaps and, more in general, to understand how the new Italian innovativeness appraisal framework was implemented.

METHODS

Appraisal reports on innovativeness were downloaded from the AIFA's website[11] as at 31 July 2020: 77 appraisal reports were found, 49 and 28 for oncology and non-oncology medicines respectively.

The following data were retrieved from the appraisal reports and inserted into an extraction template:

- final appraisal ("fully innovative", "conditionally innovative" or "not innovative");
- rank attributed to the unmet need, the added therapeutic value and the quality of evidence;
- variables that may have an influence on the final decision taken by the CTS, including:
  - the target disease: oncological (solid/hematological) disease or non-oncological disease (infectious/autoimmune/other diseases);
  - population: adult, pediatric, mixed;
  - rare disease (according to orphanet): yes or no;
  - number of "Summaries of Findings" (SoF) according to the GRADE system that reported the key information concerning the magnitudes of relative and absolute effects of the interventions examined, the amount of available evidence and the certainty (or quality) of available evidence;[12]
  - number of clinical studies considered;
  - number of randomized clinical trials (RCT), supporting the application for innovativeness;
  - number of observational studies, supporting the application for innovativeness;
- appraisal date.

We firstly calculated some descriptive statistics: frequencies and percentages for categorical variables; mean and median values, standard deviations (SD), quartiles and extreme values for continuous variables.

Afterwards, we scrutinized the role played by the above-mentioned variables on the innovativeness appraisal. Fully innovative and conditionally innovative appraisals were merged in a unique category denominated "innovative", given the limited number of appraisal reports. With reference to comparisons between groups (i.e., innovative vs. non-innovative outcome), categorical data were analyzed using a contingency table with the Chi-square or Fisher's exact test, as appropriate. Continuous data were analyzed using a Student's T-test, after checking for normal distribution (based on the Shapiro-Wilk statistic), or a Wilcoxon rank-sum test otherwise. Finally, we developed a recursive algorithm for innovativeness, using a determinist approach to scrutinize the role played by the three above-mentioned criteria (unmet need, therapeutic added value, quality of the evidence). This approach was merely data-driven and the univariate analyses on the role played by the three domains on innovative status were the starting point to create the decision tree.

Patient and Public Involvement

No patients were directly involved in this study.

RESULTS

Detailed information for each of the 77 available appraisals are reported in Supplementary Table 1.

Figure 2 shows that appraisals were equally distributed among "fully innovative" (36% of the total), "conditionally innovative" (30%) and "not innovative" (34%). Cancer medicines were more often appraised as fully innovative (39%), whereas other drugs show a higher proportion of non-innovative status (29% cancer drugs were appraised not innovative, compared to 43% non-cancer treatments), but the difference was not significant (p=0.20).

The role played on innovativeness status by the appraisal year, rare disease, target disease, target population, number of SoF, overall number of studies, number of RCT and Phase I/II studies is illustrated in Table 1.

Table 1. Variables detected on the appraisal document and innovativeness status (2017-2020).

	ALL DISEASES (n=77)				ONCOLOGY (n=49)				NON-ONCOLOGY (n=28)			
	All medicines	*Innovative*[a]	*Not innovative*	*p-value*[b]	*All medicines*	*Innovative*[a]	*Not Innovative*	*p-value*[b]	*All medicines*	*Innovative*[a]	*Not Innovative*	*p-value*[b]
CTS appraisal year	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	
2017	28 (36.4)	18 (64.3)	10 (35.7)		18 (36.7)	12 (66.7)	6 (33.3)		10 (35.7)	6 (60.0)	4 (40.0)	
2018	25 (32.5)	17 (68.0)	8 (32.0)		15 (30.6)	10 (66.7)	5 (33.3)		10 (35.7)	7 (70.0)	3 (30.0)	
2019	24 (31.2)	16 (66.7)	8 (33.3)	0.96	16 (32.7)	13 (81.2)	3 (18.8)	0.57	8 (28.6)	3 (37.5)	5 (62.5)	0.37
Rare disease												
No	34 (44.2)	20 (58.8)	14 (41.2)		23 (46.9)	17 (73.9)	6 (26.1)		11 (39.3)	3 (27.3)	8 (72.7)	
Yes	43 (55.8)	31 (72.1)	12 (27.9)	0.22	26 (53.1)	18 (69.2)	8 (30.8)	0.72	17 (60.7)	13 (76.5)	4 (23.5)	0.02
Disease												
Solid tumours	30 (39.0)	21 (70.0)	9 (30.0)		30 (61.2)	21 (70.0)	9 (30.0)		-	-	-	
Hematological malignancies	19 (24.7)	14 (73.7)	5 (26.3)		19 (38.8)	14 (73.7)	5 (26.3)	0.78	-	-	-	
Infectious diseases	5 (6.5)	3 (60.0)	2 (40.0)		-	-	-		5 (17.9)	3 (60.0)	2 (40.0)	
Autoimmune diseases	3 (3.9)	1 (33.3)	2 (66.7)		-	-	-		3 (10.7)	1 (33.3)	2 (66.7)	

Other	20 (26.0)	12 (60.0)	8 (40.0)	0.64	-	-	-		20 (71.4)	12 (60.0)	8 (40.0)	0.68
Population												
Adults only	65 (84.4)	42 (64.6)	23 (35.4)		46 (93.9)	33 (71.7)	13 (28.3)		19 (67.9)	9 (47.4)	10 (52.6)	
Pediatric or mixed	12 (15.6)	9 (75.0)	3 (25.0)	0.74	3 (6.1)	2 (66.7)	1 (33.3)	0.99	9 (32.1)	7 (77.8)	2 (22.2)	0.22
Mean number SoF (SD)	3.4 (2.9)	3.1 (2.6)	3.8 (3.4)	0.34	2.5 (2.2)	2.5 (2.2)	2.4 (2.1)	0.69	4.9 (3.4)	4.4 (2.8)	5.5 (4.0)	0.42
N studies												
1	61 (79.2)	41 (67.2)	20 (32.8)		45 (91.8)	31 (68.9)	14 (31.1)		16 (57.1)	10 (62.5)	6 (37.5)	
>1	16 (20.8)	10 (62.5)	6 (37.5)	0.72	4 (8.2)	4 (100.0)	0 (0.0)	0.31	12 (42.9)	6 (50.0)	6 (50.0)	0.51
N RCT												
0	15 (19.5)	10 (66.7)	5 (33.3)		12 (24.5)	7 (58.3)	5 (41.7)		3 (10.7)	3 (100.0)	0 (0.0)	
1	49 (63.6)	34 (69.4)	15 (30.6)		34 (69.4)	25 (73.5)	9 (26.5)		15 (53.6)	9 (60.0)	6 (40.0)	
>1	13 (16.9)	7 (53.8)	6 (46.1)	0.57	3 (6.1)	3 (100.0)	0 (0.0)	0.32	10 (35.7)	4 (40.0)	6 (60.0)	0.17
N clinical trials phase I/II												
0	59 (76.6)	38 (64.4)	21 (35.6)		37 (75.5)	28 (75.7)	9 (24.3)		22 (78.6)	10 (45.4)	12 (54.6)	
≥1	18 (23.4)	13 (72.2)	5 (27.8)	0.54	12 (24.5)	7 (58.3)	5 (41.7)	0.29	6 (21.4)	6 (100.0)	0 (0.0)	0.02

[a] Innovative status includes fully and conditionally innovative.

[b] Comparisons between innovative and non-innovative outcome were performed using a contingency table with the Chi-square or Fisher's exact test, as appropriate for categorical data. Continuous data were analyzed using a Student's T-test, after checking for normal distribution (based on the Shapiro-Wilk statistic), or a Wilcoxon rank-sum test otherwise.

CTS: Technical-scientific committee; SoF: Summaries of Findings; RCT: Randomized Clinical Trial

No significant association between innovativeness evaluation and the factors examined emerged when all types of disease were considered together. A similar proportion of appraisals was evaluated innovative with (66.1%) or without (66.7%) RCT evidence in support. Rare disease and pediatric/mixed indications were appraised innovative by a larger proportion, although not statistical significant. Furthermore, rarity of disease, and type of disease did not seem to be determinant for the innovativeness evaluation. In the non-oncological setting, rare disease status (p=0.02) and availability of one or more phase I/II studies (p=0.02) were more frequently reported in the innovative indication group. Non-oncological forms have a higher number of RCT supporting them compared to oncological ones (more than 1 RCT supporting 36% of non-oncological ones compared to approximately 6% of oncological ones).

As a second step, we investigated the role of each of the three domains on appraisals. Table 2 shows the association between unmet therapeutic need, added therapeutic need and quality of evidence and the final appraisal.

Table 2. Role played by the three domains on innovativeness status (2017-2020).

	All medicines	*Innovative*	*Not innovative*	*p-value*[b]
Unmet therapeutic need				
N	77	51	26	
Maximum (Scale=1)	10 (13.0%)	7 (70.0%)	3 (30.0%)	
Important (Scale=2)	30 (39.0%)	22 (73.3%)	8 (26.7%)	
Moderate (Scale=3)	32 (41.6%)	22 (68.7%)	10 (31.2%)	
Poor (Scale=4)	5 (6.5%)	0 (0.0%)	5 (100.0%)	0.11
Range	1 - 4	1 - 3	1 - 4	
Mean (SD)	2.4 (0.8)	2.3 (0.7)	2.7 (0.9)	0.09
Median (Range IQ)	2 (2-3)	2 (2-3)	3 (2-3)	
Added therapeutic value				
N	76 [c]	51	25 [c]	
Maximum (Scale=1)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Important (Scale=2)	25 (32.9%)	24 (96.0%)	1 (4.0%)	
Moderate (Scale=3)	31 (40.8%)	27 (87.1%)	4 (12.9%)	
Poor (Scale=4)	19 (25.0%)	0 (0.0%)	19 (100.0%)	
Very Poor (Scale=5)	1 (1.3%)	0 (0.0%)	1 (100.0%)	<0.01

Range	2 - 5		2 - 3		2 - 5	
Mean (SD)	2.9	(0.8)	2.5	(0.5)	3.8 (0.6)	<0.01
Median (Range IQ)	3	(2-4)	3	(2-3)	4 (4-4)	
Quality of clinical evidence						
(GRADE evaluation)						
N	77		51		26	
High (Scale=1)	11	(14.3%)	10	(90.9%)	1 (9.1%)	
Moderate (Scale=2)	42	(54.5%)	28	(66.7%)	14 (33.3%)	
Low (Scale=3)	18	(23.4%)	11	(61.1%)	7 (38.9%)	
Very low (Scale=4)	6	(7.8%)	2	(33.3%)	4 (66.7%)	0.11
Range	1 - 4		1 - 4		1 - 4	
Mean (SD)	2.2	(0.8)	2.1	(0.8)	2.5 (0.8)	0.03
Median (Range IQ)	2	(2-3)	2	(2-3)	2 (2-3)	

IQ: interquartile; SD: standard deviation

[a] Innovative status includes fully and conditionally innovative

[b] Comparisons between innovative and non-innovative outcome were performed using a contingency table with the Chi-square or Fisher's exact test, as appropriate for categorical data. Continuous data were analyzed using a Student's T-test, after checking for normal distribution (based on the Shapiro-Wilk statistic), or a Wilcoxon rank-sum test otherwise.

[c] For one rating (10-Nivolumab), the added therapeutic value was reported as “not assessable”.

A significant difference between innovative and not innovative outcomes was found both for the added therapeutic value ($p < 0.01$) and the quality of evidence domains ($p = 0.03$). For innovative and non-innovative indications, the added therapeutic value had an average score of 2.5 (between “Moderate” and “Important”) and 3.8 (between “Poor” and “Moderate”) respectively. The quality of evidence for innovative and non-innovative medicines had an average score of 2.1 (“Moderate”), and 2.5 (between “Low” and “Moderate”) respectively.
The average scores of unmet need for innovative and not innovative evaluations were not significantly different (p = 0.09), being respectively equal to 2.3 and 2.7 (both between “Moderate” and “Important”).
Taking into account the above-mentioned univariate findings, where added therapeutic value (p<0.01) and quality of evidence (p=0.03) were associated to innovativeness status, a data-driven decision tree using a deterministic approach was developed (Figure 3).

The flowchart illustrated by Figure 3 confirms that added therapeutic value was the most influential parameter, followed by GRADE evaluation, whereas the unmet therapeutic need had a quite limited impact on the final appraisal. When the added therapeutic value was rated as "poor" or "absent", or when the GRADE evaluation was "very low", the indication is never considered innovative. Innovativeness resulted from an at least a "moderate" added therapeutic value combined with an at least a "moderate" GRADE evaluation.
The decision tree accounted for 63 out of 77 cases (82%). As for the other 14 appraisals, 8 of them were either "conditionally innovative" or "not innovative" because they had "moderate" added therapeutic value and a "low" GRADE evaluation. The other 6 cases were given either a "full" or a "conditioned" innovativeness because they had a "moderate" added therapeutic value along with a "high" GRADE evaluation. When the final assessment was uncertain, it was not

possible to discern factors determining the final appraisal, nor to find out the driver from the characteristics of the indication, such as the disease (oncological or non-oncological) or the rarity of the disease. Finally, we found that for ultra-rare diseases (≤1 patient per 100,000 people) very low quality of evidence was not an impediment to obtain innovativeness.

DISCUSSION

The present study analyzed the new AIFA approach to appraise innovativeness for medicines. The appraisal process relies on three criteria: unmet therapeutic need, added therapeutic value, and quality of clinical evidence assessed with GRADE method. Despite the growing interest in this new appraisal process, there is still no evidence on the role played by the three criteria on the final decision, if these criteria have been consistently used overtime and if other variables do influence the innovativeness status. We found that added therapeutic value was the most influential parameter, followed by quality of evidence, whereas unmet therapeutic need had a quite limited impact on the final appraisal. It seems that a high unmet therapeutic need is perceived as a prerequisite of innovativeness, that drives the decision to apply for innovativeness, instead of being the driver of the appraisal process. Notwithstanding in five cases the unmet need had a poor rating, since its evaluation is not straightforward.[13] We investigated the potential role of other variables – namely the characteristics of the drugs and the evidence provided – that is whether there is a systematic correlation between these variables and innovativeness status. Some relationships were found: for examples, a larger proportion of drugs for rare diseases were appraised innovative. However, the statistical significance of these relationships is not reached. We have also investigated the general accuracy of the appraisal

process. Despite the high level of discretion left to the Scientific Committee in appraising the unmet need and the added therapeutic value, this process looked generally coherent.

Relying on a structured, transparent and replicable value framework to appraise new medicines is a much debated topic. Value frameworks for health technologies have been investigated by the literature[14] and huge efforts have been made to define clinical-value frameworks in specific therapeutic areas, such as cancer drugs.[15] Despite there is a general consensus that unmet need and clinical value are important value domains, it is still a matter of debate whether a threshold for minimum clinical value (meaningful clinical benefit) should be set and used by regulatory authorities,[16] as well as how other domains should be considered (e.g. patient reported outcomes and acceptability to patients) and how different domains could be aggregated to support operationally pricing based on value. [17,18]

Other European countries have relied on a formal appraisal of added therapeutic value. This is done for example in France and Germany where all new drugs and indications are appraised and added therapeutic value is ranked in five and six levels respectively.[1] Ranks are used for price / discount negotiations. In France the absolute benefit is ranked too and used to take decisions on reimbursement (introduction in the positive list and co-payment). There is evidence on the (i) coherence between ranks attributed in the two countries to the same medicine,[19] consistency between these rankings and other way of measuring added value by HTA organisations (e.g. between the added therapeutic value rank in France and QALYs – Quality Adjusted Life Years gained - in England[20]) and scientific societies[21] and the role played by the added therapeutic value in price/discount negotiation.[22] Italy is the only country in Europe where (i) innovativeness status is appraised on the grounds of a ranked unmet need, added therapeutic value and quality of the evidence, (ii) innovative medicines are provided a speeder market access

and dedicated funds and (iii) added therapeutic value rank is not used in price negotiation. As a consequence, our results, besides being the first one published on the Italian-case, cannot be fully compared with that of our countries.

The study has some limitations. Firstly, it is based on a quite small number of appraisals. This did not allow to analyze possible different patterns of association between the three innovativeness criteria and the type of innovativeness (i.e., fully or conditionally innovative). Only the availability of a larger number of innovativeness appraisals will allow to address this issue.

As already mentioned, innovativeness appraisals can be requested by the companies or spontaneously carried out by AIFA. The information on the applicant was not available and no stratified analysis could be performed, despite it would have been very interesting. We could analyze only the final appraisal published by AIFA, but we did not have any access to the applications submitted by the companies. This implies that the results of the present study cannot be considered a predictor of the response by AIFA to the applicant. However, our analysis was aimed at evaluation of the key drivers and the consistency of the AIFA decision-making process, rather than the comparison of applications submitted by the companies and final decision of AIFA.

Despite the above-mentioned limitations, our analysis has some important implications. Companies are pushed to provide solutions with an added therapeutic value and a high quality of evidence, since the latter are the driver of innovativeness, which brings important advantages for market access. We are aware that investments by the pharmaceutical companies are taken globally, but the more HTA agencies insist on clear and transparent criteria to appraise new

medicines, the higher will be the impact on the management of pipelines by the pharmaceutical companies.

The new process implemented by AIFA is also consistent with the need to rely on a pre-specified value framework enhancing transparency, accountability and, because of its intrinsic consistency, predictability of innovativeness appraisals.

Last but not least, prioritization of access through innovativeness is managed transparently, on the grounds of quite objective criteria and providing the whole stakeholders with the rationale of decision taken.

CONCLUSION

To date, the new Italian innovativeness appraisal framework looked generally coherent and can be considered an important step towards a more transparent and evidence-based management of access to medicines in Italy. In the future, the process could be further enhanced, for example including in a more structured framework patients reported outcome measures, which role is still debated, whereas at present the appraisal process mostly relies on clinical variables, and proving for an interaction between innovativeness (and its domains) appraisals and price negotiation.

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Figure 1

Criteria used to evaluate innovativeness adopted by Italian Medicines Agency.

Adapted from Recchia, 2017

* For rare disease there is the following exception: the fully innovative is attributed in the presence of at least important unmet therapeutic need and added therapeutic value in presence of at least low quality of clinical evidence.

** The innovativeness appraisal has to be decided on a case by case basis.

Figure 2

Innovative appraisals by the Italian Medicines Agency (2017-2020).

Figure 3

Deterministic decision tree based on the available innovativeness appraisals released by the Italian Medicines Agency (2017-2020).

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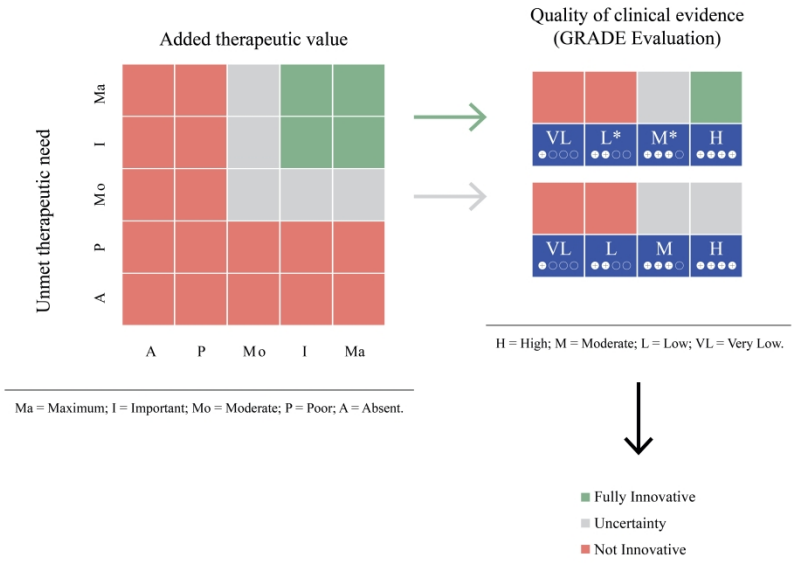

Figure 1. Criteria used to evaluate innovativeness adopted by Italian Medicines Agency.

Adapted from Recchia, 2017
* For rare disease there is the following exception: the fully innovative is attributed in the presence of at least important unmet therapeutic need and added therapeutic value in presence of at least low quality of clinical evidence.
** The innovativeness appraisal has to be decided on a case by case basis.

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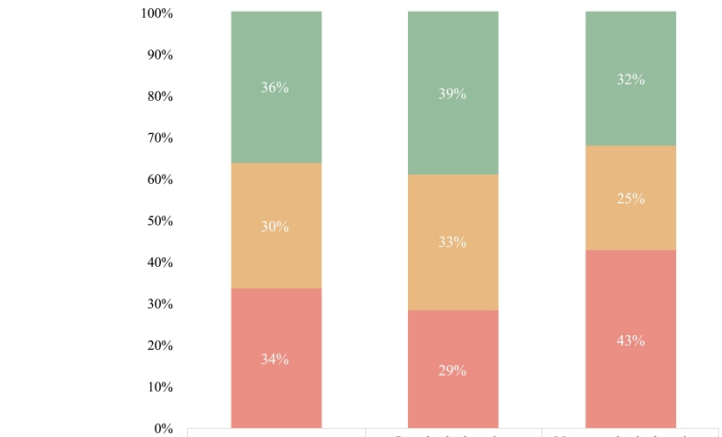

	Overall (N=77)	Oncological setting (N=49; 64%)	Non-oncological setting (N=28; 36%)
Fully Innovative	28	19	9
Conditionally Innovative	23	16	7
Not Innovative	26	14	12

Figure 2. Innovative appraisals by the Italian Medicines Agency (2017-2020)

494x361mm (300 x 300 DPI)

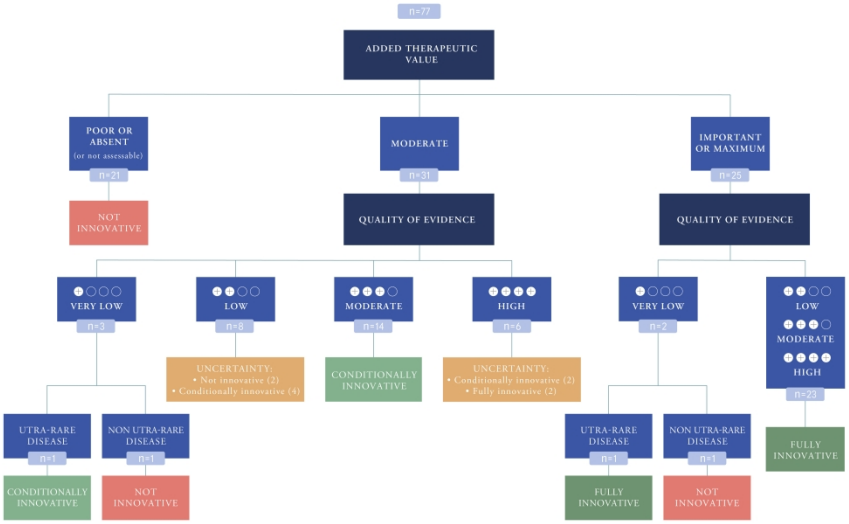

Figure 3. Deterministic decision tree based on the available innovativeness appraisals released by the Italian Medicines Agency (2017-2020)

467x304mm (300 x 300 DPI)

Supplementary Table 1 – Description of medicine innovative appraisal, ordered by date of publication on AIFA's website – *Last access 31 July 2020*

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
1	daratumumab	H	Adult	Yes	July 2017	Not innovative	Important	Moderate	Low	*Althought multiple myeloma is a rare disease (prevalence does not exceed 5 / 10,000) AIFA evaluated this medicine in a setting of non-rare disease*
2	glecaprevir and pibrentasvir	Non-Onco	Adult	No	July 2017	Fully innovative	Important	Important	Moderate	
3	obeticholic acid	Non-Onco	Adult	Yes	May 2017	Not innovative	Maximum	Poor	Low	
4	baricitinib	Non-Onco	Adult	No	June 2017	Not innovative	Moderate	Poor	High	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
5	nusinersen	Non-Onco	Pediatric	Yes	July 2017	Fully innovative	Maximum	Important	Low	
6	palbociclib	S	Adult	No	June 2017	Not innovative	Important	Poor	Moderate	
7	palbociclib	S	Adult	No	June 2017	Conditionally innovative	Moderate	Moderate	Moderate	
8	cenegermin	Non-Onco	Adult	Yes	November 2017	Fully innovative	Important	Important	Low	
9	ceftazidime / avibactam	Non-Onco	Adult	No	July 2017	Not innovative	Important	Poor	Low	
10	nivolumab	S	Adult	No	September 2017	Not innovative	Important	N/A	Low	*The added therapeutic value in this indication was considered not assessable*
11	allogeneic t cells genetically modified	H	Adult	Yes	September 2017	Not innovative	Moderate	Moderate	Very low	
12	daratumumab	H	Adult	Yes	October 2017	Fully innovative	Moderate	Important	Moderate	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
13	sofosbuvir/ velpatasvir/ voxilaprevir	Non-Onco	Adult	No	July 2017	Fully innovative	Important	Important	Moderate	
14	adalimumab	Non-Onco	Adult	Yes	November 2017	Conditionally innovative	Important	Moderate	Moderate	
15	lenalidomide	H	Adult	Yes	September 2017	Conditionally innovative	Moderate	Moderate	Moderate	
16	inotuzumab ozagamicin	H	Adult	Yes	October 2017	Conditionally innovative	Moderate	Moderate	Moderate	
17	atezolizumab	S	Adult	No	November 2017	Fully innovative	Important	Moderate	High	
18	bezlotoxumab	Non-Onco	Adult	No	October 2017	Not innovative	Important	Moderate	Low	
19	dinutuximab beta	S	Mixed	Yes	February 2018	Fully innovative	Maximum	Important	Moderate	
20	dinutuximab beta	S	Mixed	Yes	February 2018	Not innovative	Maximum	Important	Very low	
21	alectinib	S	Adult	No	January 2018	Conditionally innovative	Moderate	Moderate	Moderate	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
22	alectinib	S	Adult	No	January 2018	Fully innovative	Moderate	Important	Moderate	
23	nivolumab	S	Adult	No	November 2017	Conditionally innovative	Important	Moderate	Moderate	
24	midostaurin	H	Adult	Yes	December 2017	Fully innovative	Moderate	Important	Moderate	
25	midostaurin	H	Adult	Yes	December 2017	Not innovative	Important	Poor	Low	
26	ibrutinib	H	Adult	Yes	October 2017	Conditionally innovative	Moderate	Moderate	Moderate	
27	dupilumab	Non-Onco	Adult	No	January 2018	Fully innovative	Important	Moderate	High	
28	ocrelizumab	Non-Onco	Adult	No	February 2018	Not innovative	Maximum	Poor	Moderate	
29	letermovir	Non-Onco	Adult	Yes	February 2018	Fully innovative	Moderate	Important	High	
30	avelumab	S	Adult	Yes	January 2018	Conditionally innovative	Important	Moderate	Low	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
31	canakinumab	Non-Onco	Mixed	Yes	December 2017	Conditionally innovative	Important	Moderate	Moderate	
32	ibrutinib	H	Adult	Yes	July 2017	Not innovative	Poor	Poor	Moderate	
33	ribociclib	S	Adult	No	November 2017	Conditionally innovative	Moderate	Moderate	Moderate	
34	nivolumab	H	Adult	Yes	July 2017	Conditionally innovative	Maximum	Moderate	Low	
35	niraparib	S	Adult	Yes	January 2018	Conditionally innovative	Important	Moderate	Moderate	
36	regorafenib	S	Adult	No	February 2018	Conditionally innovative	Maximum	Moderate	High	
37	emicizumab	Non-Onco	Mixed	Yes	June 2018	Fully innovative	Moderate	Important	Low	
38	ethyl telotristat	S	Adult	Yes	January 2018	Not innovative	Important	Poor	Moderate	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
39	liposomal daunorubicin hydrochloride / cytarabine	H	Adult	Yes	November 2018	Fully innovative	Moderate	Important	Moderate	
40	pembrolizumab	S	Adult	No	May 2019	Fully innovative	Moderate	Important	High	
41	tocilizumab	Non-Onco	Adult	Yes	July 2018	Conditionally innovative	Moderate	Moderate	Moderate	
42	daratumumab	H	Adult	Yes	October 2017	Fully innovative	Moderate	Important	Moderate	
43	cladribine	Non-Onco	Adult	No	April 2018	Not innovative	Moderate	Poor	Very low	
44	lutetium oxodotreotide	S	Adult	Yes	March 2018	Fully innovative	Important	Important	Low	
45	darvadstrocel	Non-Onco	Adult	Yes	April 2019	Not innovative	Moderate	Poor	Low	
46	cysteamine	Non-Onco	Mixed	Yes	January 2018	Not innovative	Poor	Moderate	Very low	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
47	obinutuzumab	H	Adult	Yes	March 2018	Not innovative	Poor	Poor	Moderate	
48	pembrolizumab	S	Adult	No	June 2018	Conditionally innovative	Important	Moderate	High	
49	pembrolizumab	H	Adult	Yes	November 2017	Conditionally innovative	Maximum	Moderate	Low	
50	pertuzumab	S	Adult	No	November 2018	Not innovative	Moderate	Poor	Moderate	
51	tisagenlecleucel	H	Mixed	Yes	January 2019	Fully innovative	Important	Important	Moderate	
52	tisagenlecleucel	H	Adult	Yes	January 2019	Fully innovative	Important	Important	Low	
53	burosumab	Non-Onco	Pediatric	Yes	December 2018	Conditionally innovative	Important	Moderate	Low	
54	durvalumab	S	Adult	No	March 2019	Fully innovative	Important	Important	Moderate	
55	lenvatinib	S	Adult	Yes	April 2019	Not innovative	Important	Absent	Moderate	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
56	brentuximab vedotin	H	Adult	Yes	April 2018	Conditionally innovative	Moderate	Moderate	Moderate	
57	pembrolizumab	S	Adult	No	May 2019	Fully innovative	Important	Moderate	High	
58	pembrolizumab	S	Adult	No	May 2019	Fully innovative	Moderate	Important	Moderate	
59	nivolumab	S	Adult	No	April 2019	Fully innovative	Important	Moderate	High	
60	osimertinib	S	Adult	No	February 2019	Fully innovative	Moderate	Important	Moderate	
61	axicabtagene ciloleucel	H	Adult	Yes	January 2019	Fully innovative	Important	Important	Moderate	
62	dabrafenib	S	Adult	No	April 2019	Fully innovative	Important	Important	High	
63	trametinib	S	Adult	No	April 2019	Fully innovative	Important	Important	High	
64	doravirina/ lamivudina/ tenofovir disoproxil	Non-Onco	Adult	No	May 2019	Not innovative	Poor	Poor	Moderate	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
65	doravirine	Non-Onco	Adult	No	May 2019	Not innovative	Poor	Poor	Moderate	
66	venetoclax	H	Adult	Yes	April 2019	Conditionally innovative	Moderate	Moderate	Moderate	
67	abemaciclib	S	Adult	No	May 2019	Conditionally innovative	Moderate	Moderate	Moderate	
68	caplacizumab	Non-Onco	Adult	Yes	February 2019	Conditionally innovative	Moderate	Moderate	Low	
69	patisiran	Non-Onco	Adult	Yes	November 2018	Fully innovative	Important	Important	Moderate	
70	emicizumab	Non-Onco	Mixed	Yes	October 2019	Conditionally innovative	Moderate	Moderate	Low	
71	metreleptin	Non-Onco	Mixed	Yes	February 2019	Conditionally innovative	Maximum	Moderate	Very low	*Ultra-rare disease*
72	abiraterone acetate	S	Adult	No	May 2018	Not innovative	Moderate	Poor	Moderate	
73	alirocumab	Non-Onco	Adult	No	November 2019	Not innovative	Moderate	Poor	Moderate	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
74	encorafenib	S	Adult	No	May 2019	Not innovative	Moderate	Poor	Moderate	
75	binimetinib	S	Adult	No	May 2019	Not innovative	Moderate	Poor	Moderate	
76	lanadelumab	Non-Onco	Mixed	Yes	December 2019	Not innovative	Moderate	Poor	Moderate	
77	cerliponase alfa	Non-Onco	Pediatric	Yes	December 2018	Fully innovative	Maximum	Important	Very low	*Ultra-rare disease*

** according to orphanet*

AIFA: italian medicines agency; CTS: techical-scientific commitee; H: hematological malignancies; S: solid tumor; onco: oncological disease; non-onco: non oncological disease

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KEY DRIVERS OF INNOVATIVENESS APPRAISAL FOR MEDICINES: THE ITALIAN EXPERIENCE AFTER THE ADOPTION OF THE NEW RANKING SYSTEM

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KEY DRIVERS OF INNOVATIVENESS APPRAISAL FOR MEDICINES: THE ITALIAN EXPERIENCE AFTER THE ADOPTION OF THE NEW RANKING SYSTEM

Running title: Innovativeness appraisal for medicines in Italy

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ABSTRACT

Objective: In 2017, the Italian Medicines Agency (AIFA) introduced a standardized process to appraise innovativeness of medicines. Innovative medicines are provided speeder market access and dedicated funds. Innovativeness criteria are: unmet therapeutic need, added therapeutic value and quality of the evidence (GRADE method). We investigated the role played by these three criteria on the final decision aimed to understand how the new Italian innovativeness appraisal framework was implemented.

Design: A desk research gathered AIFA's appraisals reports on innovativeness and data analyses were conducted. No patients were directly involved in this study.

Setting and Participants: We scrutinized all 77 appraisals reports available on AIFA's website (2017-2020).

Primary and secondary outcome measures: The impact of the three domains on final decision was investigated through a series of univariate analyses.

Results: Among 77 appraisal reports on innovativeness available, 49 (64%) and 28 (36%) were for oncology and non-oncology medicines, respectively. The appraisals were equally distributed among "fully innovative" (36%), "conditionally innovative" (30%) and "not innovative" (34%). Added therapeutic value was the most important driver on innovativeness decision, followed by quality of the evidence. Drugs for rare diseases and with pediatric/mixed indications were appraised 'innovative' by a larger proportion, but no statistical significance was found.

Conclusions: Despite some limitations, including the moderate number of appraisals, this paper provides an insight into the determinants of innovativeness appraisals for medicines in Italy and the accurancy of the appraisal process. This has important implications in terms of transparency and accountability in the prioritization process applied to innovative medicines.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is an original, up to date analysis of the new National Drugs Agency appraisals framework for drug innovativeness in the Italian setting
- This study was based on a limited number of appraisals, but we systematically considered all the available ones
- The relatively small number of appraisals did not allow to analyze possible different patterns of association between the three innovativeness criteria and the type of innovativeness (i.e., fully or conditionally innovative)

INTRODUCTION

Market Access for pharmaceuticals in Italy is managed by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA). AIFA, differently from most other European Countries medicines agencies, have both regulatory and access competences.[1] The latter include the negotiation of reimbursement, ex-factory price and managed entry agreements and the appraisal of innovativeness status, possibly required by the pharmaceutical companies at market launch or autonomously carried out by AIFA.[2] Innovativeness status has some advantages from an access perspective, including two dedicated funds (one for cancer medicines and the other for non-cancer medicines) and immediate access to regional markets.

The criteria to get innovativeness status, which can be attributed only to drugs indicated for serious illnesses (*life-threatening diseases; diseases producing frequent hospitalizations or causing disabilities that can seriously compromise quality of life*") are the unmet therapeutic need, the added therapeutic value and the quality of the evidence (Determina AIFA 519/2017).[3]

The **unmet therapeutic need** is rated as:

- *Maximum*: there are no alternatives for that specific indication;
- *Important*: there are a few alternatives, but with no impact on clinically relevant endpoints;
- *Moderate*: there are alternatives with a limited and/or uncertain or unreliable impact on clinically relevant endpoints;
- *Poor:* there are alternatives for the same indication with clinically proven reliable results;
- *Absent*: there are alternatives for the same indication with an important impact on the natural history of the disease.

The added **therapeutic value**, that refers to clinical benefit, can be rated as:

- *Maximum*: the new drug has proven larger efficacy than any possible existing alternatives. In this case, the treatment is able to either cure the illness or significantly alter its natural history;
- *Important*: the new drug has a proven larger efficacy measured on clinically relevant endpoints, decreases the risk of invalidating or fatal complications, avoids highly dangerous clinical procedures or has more favorable risk/benefit (R/B) ratio than any available alternatives. In a subset of patients, the treatment either modifies the natural history of the disease or is beneficial in other clinically significant ways, e.g. in terms of quality of life or disease-free intervals, when compared to available alternatives;
- *Moderate*: the new drug has a larger efficacy than any available alternatives, but it is only moderate or only proven in some subsets of patients, with limited impact on the quality of life;
- *Poor*: the new drug has either a limited improvement of efficacy or has been proven on endpoints which are not clinically relevant. Minor advantages, e.g. more acceptable administration route;
- Absent: the new drug has no relevant benefit when compared to other available treatments.

Endpoints relevance has been specified for cancer medicines, being overall survival (OS) considered the gold standard, and the lack of OS data needed to justify. The document quotes that progression-free survival (PFS), disease-free survival (DFS), full response time or other surrogated endpoints (with already established clinical benefits) may be taken into account,

according to indication and settings. Toxicity is also considered to evaluate the treatment's adequacy.

To appraise the **quality of evidence**, AIFA has chosen the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.[4] According to this approach, the quality of clinical evidence can be graded as high, moderate, low or very low. The choice of GRADE methodology was aimed at improving the transparency and reproducibility of the appraisal process; this structured and flexible methodological tool provides a systematic approach in the assessment and is meant to minimize biases and improve consistency of the decisions.[5]

The innovativeness is appraised per indication, and the innovativeness status lasts three years. The appraisal model represents a common framework for all indications, even if safeguard clauses are provided for rare indications where the quality of the evidence is more likely to be lower.

The industry usually applies for innovativeness, even if AIFA can proceed to evaluate it regardless of the industry' application. The innovativeness request is appraised by the AIFA's Technical-Scientific Committee (CTS). CTS may decide for full innovativeness, conditional innovativeness or non-innovative. Conditionally innovative medicines share with fully innovative medicines only the immediate access to regional markets. Conditional innovativeness is granted when the evidence is not sufficiently mature to provide a full innovativeness status and lasts 18 months.

Despite the growing interest in this new criteria and the relevant appraisal process,[6] to our knowledge only preliminary descriptive analyses (based on less of 20 innovativeness appraisals updated to 2018) were available[7–9] and no clear and robust evidence emerged on the role

played by the three criteria on the final decision, if these criteria have been consistently used over time and if other variables influence the innovativeness status.

Our analyses, based on available innovativeness appraisals updated to July 2020, aim to cover these information gaps and, more in general, to understand how the new Italian innovativeness appraisal framework was implemented.

METHODS

The new decision rule adopted by AIFA (Figure 1)[10] consists to grant innovativeness if both unmet need and added therapeutic value are graded "Maximum" or "Important" and the quality of evidence is rated "High" (green zone). Conversely, if the unmet need or the added therapeutic value are graded "Poor" or "Absent", or the quality of evidence is rated "Low" or "Very Low" innovativeness will be not granted (red zone). For rare indications, the innovative status may be granted even if the quality of evidence is graded "Low", but the unmet need and the added therapeutic value are both at least "Important". To note, in the intermediate situations (grey zone) there is uncertainty about innovation status, and AIFA decides case-by-case.

Pharmaceutical companies are informed by AIFA on the intended final appraisal and can rebut on appraisals in ten days. The final appraisal is published on the AIFA's website, together with a short description of the rationale behind the decision taken (www.aifa.gov.it). These appraisals are written in Italian only. An English version should be desirable to allow greater dissemination of information outside Italy.

Appraisal reports on innovativeness were downloaded from the AIFA's website[11] as at 31 July 2020: 77 appraisal reports were found, 49 and 28 for oncology and non-oncology medicines, respectively.

The following data were retrieved from the appraisal reports and inserted into an extraction template:

- final appraisal ("fully innovative", "conditionally innovative" or "not innovative");
- rank attributed to the unmet need, the added therapeutic value and the quality of evidence;
- variables that may have an influence on the final decision taken by the CTS, including:

- the target disease: oncological (solid/hematological) disease or non-oncological disease (infectious/autoimmune/other diseases);
- population: adult, pediatric, mixed;
- rare disease (according to orphanet): yes or no;
- number of "Summaries of Findings" (SoF) according to the GRADE system that reported the key information concerning the magnitudes of relative and absolute effects of the interventions examined, the amount of available evidence and the certainty (or quality) of available evidence;[12]
- number of clinical studies considered;
- number of randomized clinical trials (RCT), supporting the application for innovativeness;
- number of observational studies, supporting the application for innovativeness;

- appraisal date.

We firstly calculated some descriptive statistics: frequencies and percentages for categorical variables; mean and median values, standard deviations (SD), quartiles and extreme values for continuous variables.

Afterwards, we scrutinized the role played by the above-mentioned variables on the innovativeness appraisal. Fully innovative and conditionally innovative appraisals were merged in a unique category denominated "innovative", given the limited number of appraisal reports. With reference to comparisons between groups (i.e., innovative vs. non-innovative outcome), categorical data were analyzed using a contingency table with the Chi-square or Fisher's exact test, as appropriate. Continuous data were analyzed using a Student's T-test, after checking for normal distribution (based on the Shapiro-Wilk statistic), or a Wilcoxon rank-sum test otherwise.

With reference to the primary aim of this study, i.e., the role played by the three domains on innovativeness status (innovativeness vs not innovativeness), we decided *a-priori* to compare groups by using the test for continuous variables, that has a higher power to detect possible differences in this set of preliminary analyses. In fact, the Fisher's exact test has low power to detect associations, i.e., the probability of obtaining false negative conclusions (type II error) is high.

Finally, we developed a recursive algorithm for innovativeness, using a determinist approach to scrutinize the role played by the three above-mentioned criteria (unmet need, therapeutic added value, quality of the evidence). This approach was merely data-driven and the univariate analyses on the role played by the three domains on innovative status were the starting point to create the decision tree.

Patient and Public Involvement

No patients were directly involved in this study.

RESULTS

Detailed information for each of the 77 available appraisals are reported in Supplementary Table 1.

Figure 2 shows that appraisals were equally distributed among "fully innovative" (36% of the total), "conditionally innovative" (30%) and "not innovative" (34%). Cancer medicines were more often appraised as fully innovative (39%), whereas other drugs show a higher proportion of non-innovative status (29% cancer drugs were appraised not innovative, compared to 43% non-cancer treatments), but the difference was not significant (p=0.20).

The role played on innovativeness status by the appraisal year, rare disease, target disease, target population, number of SoF, overall number of studies, number of RCT and Phase I/II studies is illustrated in Table 1.

Table 1. Variables detected on the appraisal document and innovativeness status (2017-2020).

	ALL DISEASES (n=77)				ONCOLOGY (n=49)				NON-ONCOLOGY (n=28)			
	All medicines	*Innovative*[a]	*Not innovative*	*p-value*[b]	*All medicines*	*Innovative*[a]	*Not Innovative*	*p-value*[b]	*All medicines*	*Innovative*[a]	*Not Innovative*	*p-value*[b]
CTS appraisal year	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	
2017	28 (36.4)	18 (64.3)	10 (35.7)		18 (36.7)	12 (66.7)	6 (33.3)		10 (35.7)	6 (60.0)	4 (40.0)	
2018	25 (32.5)	17 (68.0)	8 (32.0)		15 (30.6)	10 (66.7)	5 (33.3)		10 (35.7)	7 (70.0)	3 (30.0)	
2019	24 (31.2)	16 (66.7)	8 (33.3)	0.96	16 (32.7)	13 (81.2)	3 (18.8)	0.57	8 (28.6)	3 (37.5)	5 (62.5)	0.37
Rare disease												
No	34 (44.2)	20 (58.8)	14 (41.2)		23 (46.9)	17 (73.9)	6 (26.1)		11 (39.3)	3 (27.3)	8 (72.7)	
Yes	43 (55.8)	31 (72.1)	12 (27.9)	0.22	26 (53.1)	18 (69.2)	8 (30.8)	0.72	17 (60.7)	13 (76.5)	4 (23.5)	0.02
Disease												
Solid tumours	30 (39.0)	21 (70.0)	9 (30.0)		30 (61.2)	21 (70.0)	9 (30.0)		-	-	-	
Hematological malignancies	19 (24.7)	14 (73.7)	5 (26.3)		19 (38.8)	14 (73.7)	5 (26.3)	0.78	-	-	-	
Infectious diseases	5 (6.5)	3 (60.0)	2 (40.0)		-	-	-		5 (17.9)	3 (60.0)	2 (40.0)	

Autoimmune diseases	3 (3.9)	1 (33.3)	2 (66.7)		-	-	-		3 (10.7)	1 (33.3)	2 (66.7)	
Other	20 (26.0)	12 (60.0)	8 (40.0)	0.64	-	-	-		20 (71.4)	12 (60.0)	8 (40.0)	0.68
Population												
Adults only	65 (84.4)	42 (64.6)	23 (35.4)		46 (93.9)	33 (71.7)	13 (28.3)		19 (67.9)	9 (47.4)	10 (52.6)	
Pediatric or mixed	12 (15.6)	9 (75.0)	3 (25.0)	0.74	3 (6.1)	2 (66.7)	1 (33.3)	0.99	9 (32.1)	7 (77.8)	2 (22.2)	0.22
Mean number SoF (SD)	3.4 (2.9)	3.1 (2.6)	3.8 (3.4)	0.34	2.5 (2.2)	2.5 (2.2)	2.4 (2.1)	0.69	4.9 (3.4)	4.4 (2.8)	5.5 (4.0)	0.42
N studies												
1	61 (79.2)	41 (67.2)	20 (32.8)		45 (91.8)	31 (68.9)	14 (31.1)		16 (57.1)	10 (62.5)	6 (37.5)	
>1	16 (20.8)	10 (62.5)	6 (37.5)	0.72	4 (8.2)	4 (100.0)	0 (0.0)	0.31	12 (42.9)	6 (50.0)	6 (50.0)	0.51
N RCT												
0	15 (19.5)	10 (66.7)	5 (33.3)		12 (24.5)	7 (58.3)	5 (41.7)		3 (10.7)	3 (100.0)	0 (0.0)	
1	49 (63.6)	34 (69.4)	15 (30.6)		34 (69.4)	25 (73.5)	9 (26.5)		15 (53.6)	9 (60.0)	6 (40.0)	
>1	13 (16.9)	7 (53.8)	6 (46.1)	0.57	3 (6.1)	3 (100.0)	0 (0.0)	0.32	10 (35.7)	4 (40.0)	6 (60.0)	0.17
N clinical trials phase I/II												
0	59 (76.6)	38 (64.4)	21 (35.6)		37 (75.5)	28 (75.7)	9 (24.3)		22 (78.6)	10 (45.4)	12 (54.6)	

≥1	18 (23.4)	13 (72.2)	5 (27.8)	0.54	12 (24.5)	7 (58.3)	5 (41.7)	0.29	6 (21.4)	6 (100.0)	0 (0.0)	0.02

[a] Innovative status includes fully and conditionally innovative.

[b] Comparisons between innovative and non-innovative outcome were performed using a contingency table with the Chi-square or Fisher's exact test, as appropriate for categorical data. Continuous data were analyzed using a Student's T-test, after checking for normal distribution (based on the Shapiro-Wilk statistic), or a Wilcoxon rank-sum test otherwise.

CTS: Technical-scientific committee; SoF: Summaries of Findings; RCT: Randomized Clinical Trial

No significant association between innovativeness evaluation and the factors examined emerged when all types of disease were considered together. A similar proportion of appraisals was evaluated innovative with (66.1%) or without (66.7%) RCT evidence in support. Rare disease and pediatric/mixed indications were appraised innovative by a larger proportion, although not statistical significant. Furthermore, rarity of disease, and type of disease did not seem to be determinant for the innovativeness evaluation. In the non-oncological setting, rare disease status (p=0.02) and availability of one or more phase I/II studies (p=0.02) were more frequently reported in the innovative indication group. Non-oncological forms have a higher number of RCT supporting them compared to oncological ones (more than 1 RCT supporting 36% of non-oncological ones compared to approximately 6% of oncological ones).

As a second step, we investigated the role of each of the three domains on appraisals. Table 2 shows the association between unmet therapeutic need, added therapeutic need and quality of evidence and the final appraisal.

Table 2. Role played by the three domains on innovativeness status (2017-2020).

	All medicines	*Innovative*	*Not innovative*	*p-value*[b]
Unmet therapeutic need				
N	77	51	26	
Maximum (Scale=1)	10 (13.0%)	7 (70.0%)	3 (30.0%)	
Important (Scale=2)	30 (39.0%)	22 (73.3%)	8 (26.7%)	
Moderate (Scale=3)	32 (41.6%)	22 (68.7%)	10 (31.2%)	
Poor (Scale=4)	5 (6.5%)	0 (0.0%)	5 (100.0%)	
Range	1 - 4	1 - 3	1 - 4	
Mean (SD)	2.4 (0.8)	2.3 (0.7)	2.7 (0.9)	0.09
Median (Range IQ)	2 (2-3)	2 (2-3)	3 (2-3)	
Added therapeutic value				
N	76 [c]	51	25 [c]	
Maximum (Scale=1)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Important (Scale=2)	25 (32.9%)	24 (96.0%)	1 (4.0%)	
Moderate (Scale=3)	31 (40.8%)	27 (87.1%)	4 (12.9%)	
Poor (Scale=4)	19 (25.0%)	0 (0.0%)	19 (100.0%)	
Very Poor (Scale=5)	1 (1.3%)	0 (0.0%)	1 (100.0%)	
Range	2 - 5	2 - 3	2 - 5	

Mean (SD)	2.9	(0.8)	2.5	(0.5)	3.8	(0.6)	<0.01
Median (Range IQ)	3	(2-4)	3	(2-3)	4	(4-4)	
Quality of clinical evidence (GRADE evaluation)							
N	77		51		26		
High (Scale=1)	11	(14.3%)	10	(90.9%)	1	(9.1%)	
Moderate (Scale=2)	42	(54.5%)	28	(66.7%)	14	(33.3%)	
Low (Scale=3)	18	(23.4%)	11	(61.1%)	7	(38.9%)	
Very low (Scale=4)	6	(7.8%)	2	(33.3%)	4	(66.7%)	
Range	1 - 4		1 - 4		1 - 4		
Mean (SD)	2.2	(0.8)	2.1	(0.8)	2.5	(0.8)	0.03
Median (Range IQ)	2	(2-3)	2	(2-3)	2	(2-3)	

IQ: interquartile; SD: standard deviation

[a] Innovative status includes fully and conditionally innovative

[b] Comparisons between innovative and non-innovative outcome were performed using a Student's T-test, after checking for normal distribution (based on the Shapiro-Wilk statistic), or a Wilcoxon rank-sum test otherwise.

[c] For one rating (10-Nivolumab), the added therapeutic value was reported as "not assessable".

A significant difference between innovative and not innovative outcomes was found both for the added therapeutic value ($p < 0.01$) and the quality of evidence domains ($p = 0.03$). For innovative and non-innovative indications, the added therapeutic value had an average score of 2.5 (between "Moderate" and "Important") and 3.8 (between "Poor" and "Moderate") respectively. The quality of evidence for innovative and non-innovative medicines had an average score of 2.1 ("Moderate"), and 2.5 (between "Low" and "Moderate") respectively. The average scores of unmet need for innovative and not innovative evaluations were not significantly different (p = 0.09), being respectively equal to 2.3 and 2.7 (both between "Moderate" and "Important").

Taking into account the above-mentioned univariate findings, where added therapeutic value (p<0.01) and quality of evidence (p=0.03) were associated to innovativeness status, a data-driven decision tree using a deterministic approach was developed (Supplementary Figure 1). The decision tree did not explicate all the appraisals final decision but accounted for 63 out of 77 cases (82%). As for the other 14 appraisals, 8 of them were either "conditionally innovative" or "not innovative" because they had "moderate" added therapeutic value and a "low" GRADE evaluation. The other 6 cases were given either a "full" or a "conditioned" innovativeness because they had a "moderate" added therapeutic value along with a "high" GRADE evaluation. When the final assessment was uncertain, it was not possible to discern factors determining the final appraisal, nor to find out the driver from the characteristics of the indication, such as the disease (oncological or non-oncological) or the rarity of the disease. Finally, we found that for ultra-rare diseases (≤1 patient per 100,000 people) very low quality of evidence was not an impediment to obtain innovativeness.

DISCUSSION

The present study analyzed the new AIFA approach to appraise innovativeness for medicines. The appraisal process relies on three criteria: unmet therapeutic need, added therapeutic value, and quality of clinical evidence assessed with GRADE method. Despite the growing interest in this new

appraisal process, there is still no evidence on the role played by the three criteria on the final decision, if these criteria have been consistently used overtime and if other variables do influence the innovativeness status. We found that added therapeutic value was the most influential parameter, followed by quality of evidence, whereas unmet therapeutic need had a quite limited impact on the final appraisal. It seems that a high unmet therapeutic need is perceived as a prerequisite of innovativeness, that drives the decision to apply for innovativeness, instead of being the driver of the appraisal process. Notwithstanding in five cases the unmet need had a poor rating, since its evaluation is not straightforward.[13] We investigated the potential role of other variables – namely the characteristics of the drugs and the evidence provided – that is whether there is a systematic correlation between these variables and innovativeness status. Some relationships were found: for examples, a larger proportion of drugs for rare diseases were appraised innovative. However, the statistical significance of these relationships is not reached. We have also investigated the general accuracy of the appraisal process. Despite the high level of discretion left to the Scientific Committee in appraising the unmet need and the added therapeutic value, this process looked generally coherent. Relying on a structured, transparent and replicable value framework to appraise new medicines is a much debated topic. Value frameworks for health technologies have been investigated by the literature[14] and huge efforts have been made to define clinical-value frameworks in specific therapeutic areas, such as cancer drugs.[15] Despite there is a general consensus that unmet need and clinical value are important value domains, it is still a matter of debate whether a threshold for minimum clinical value (meaningful clinical benefit) should be set and used by regulatory authorities,[16] as well as how other domains should be considered (e.g. patient reported outcomes and acceptability to patients) and how different domains could be aggregated to support operationally pricing based on value. [17,18]

Other European countries have relied on a formal appraisal of added therapeutic value. This is done for example in France and Germany where all new drugs and indications are appraised and added

therapeutic value is ranked in five and six levels respectively.[1] Ranks are used for price / discount negotiations. In France the absolute benefit is ranked too and used to take decisions on reimbursement (introduction in the positive list and co-payment). There is evidence on the (i) coherence between ranks attributed in the two countries to the same medicine,[19] consistency between these rankings and other way of measuring added value by HTA organisations (e.g. between the added therapeutic value rank in France and QALYs – Quality Adjusted Life Years gained - in England[20]) and scientific societies[21] and the role played by the added therapeutic value in price/discount negotiation.[22] Italy is the only country in Europe where (i) innovativeness status is appraised on the grounds of a ranked unmet need, added therapeutic value and quality of the evidence, (ii) innovative medicines are provided a speeder market access and dedicated funds and (iii) added therapeutic value rank is not used in price negotiation. As a consequence, our results, besides being the first one published on the Italian-case, cannot be fully compared with that of our countries.

The study has some limitations. Firstly, it is based on a quite small number of appraisals. This did not allow to analyze possible different patterns of association between the three innovativeness criteria and the type of innovativeness (i.e., fully or conditionally innovative). Only the availability of a larger number of innovativeness appraisals will allow to address this issue.

As already mentioned, innovativeness appraisals can be requested by the companies or spontaneously carried out by AIFA. The information on the applicant was not available and no stratified analysis could be performed, despite it would have been very interesting. We could analyze only the final appraisal published by AIFA, but we did not have any access to the applications submitted by the companies. This implies that the results of the present study cannot be considered a predictor of the response by AIFA to the applicant. However, our analysis was aimed at evaluation of the key drivers and the consistency of the AIFA decision-making process, rather than the comparison of applications submitted by the companies and final decision of AIFA.

Despite the above-mentioned limitations, our analysis has some important implications. Companies are pushed to provide solutions with an added therapeutic value and a high quality of evidence, since the latter are the driver of innovativeness, which brings important advantages for market access. We are aware that investments by the pharmaceutical companies are taken globally, but the more HTA agencies insist on clear and transparent criteria to appraise new medicines, the higher will be the impact on the management of pipelines by the pharmaceutical companies.

The new process implemented by AIFA is also consistent with the need to rely on a pre-specified value framework enhancing transparency, accountability and, because of its intrinsic consistency, predictability of innovativeness appraisals.

Last but not least, prioritization of access through innovativeness is managed transparently, on the grounds of quite objective criteria and providing the whole stakeholders with the rationale of decision taken.

CONCLUSION

To date, the new Italian innovativeness appraisal framework looked generally coherent and can be considered an important step towards a more transparent and evidence-based management of access to medicines in Italy. In the future, the process could be further enhanced, for example including in a more structured framework patients reported outcome measures, which role is still debated, whereas at present the appraisal process mostly relies on clinical variables, and proving for an interaction between innovativeness (and its domains) appraisals and price negotiation.

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Figure Legend

Figure 1 – Criteria used to evaluate innovativeness adopted by the Italian Medicines Agency. Adapted from Recchia, 2017

Figure 2 – Innovative appraisals by the Italian Medicines Agency (2017-2020)

Supplementary Figure 1 - Deterministic decision tree based on the available innovativeness appraisals released by the Italian Medicines Agency (2017-2020)

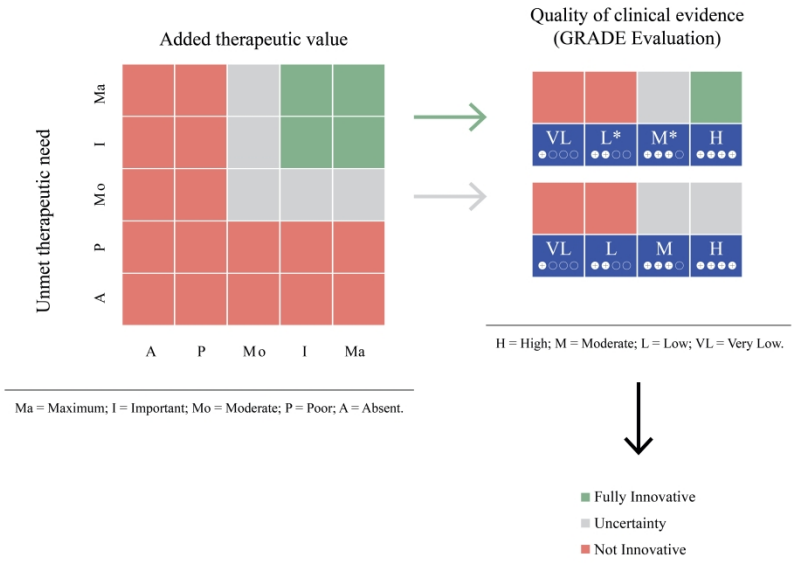

Figure 1. Criteria used to evaluate innovativeness adopted by Italian Medicines Agency.

Adapted from Recchia, 2017
* For rare disease there is the following exception: the fully innovative is attributed in the presence of at least important unmet therapeutic need and added therapeutic value in presence of at least low quality of clinical evidence.
** The innovativeness appraisal has to be decided on a case by case basis.

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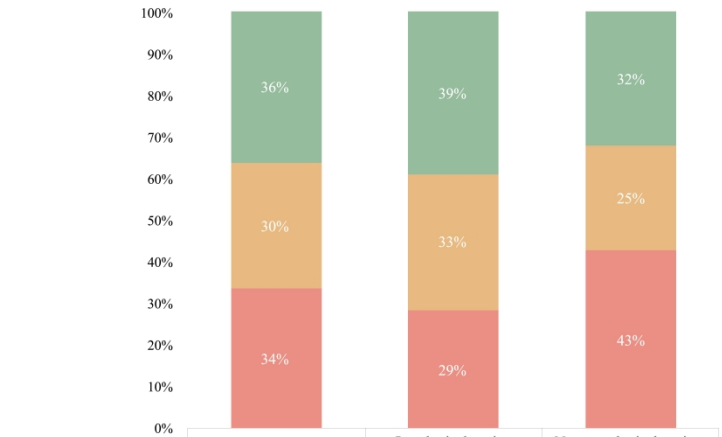

	Overall (N=77)	Oncological setting (N=49; 64%)	Non-oncological setting (N=28; 36%)
Fully Innovative	28	19	9
Conditionally Innovative	23	16	7
Not Innovative	26	14	12

Figure 2. Innovative appraisals by the Italian Medicines Agency (2017-2020)

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Supplementary Table 1 – Description of medicine innovative appraisal, ordered by date of publication on AIFA's website – *Last access 31 July 2020*

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
1	daratumumab	H	Adult	Yes	July 2017	Not innovative	Important	Moderate	Low	*Althought multiple myeloma is a rare disease (prevalence does not exceed 5 / 10,000) AIFA evaluated this medicine in a setting of non-rare disease*
2	glecaprevir and pibrentasvir	Non-Onco	Adult	No	July 2017	Fully innovative	Important	Important	Moderate	
3	obeticholic acid	Non-Onco	Adult	Yes	May 2017	Not innovative	Maximum	Poor	Low	
4	baricitinib	Non-Onco	Adult	No	June 2017	Not innovative	Moderate	Poor	High	
5	nusinersen	Non-Onco	Pediatric	Yes	July 2017	Fully innovative	Maximum	Important	Low	
6	palbociclib	S	Adult	No	June 2017	Not innovative	Important	Poor	Moderate	
7	palbociclib	S	Adult	No	June 2017	Conditionally innovative	Moderate	Moderate	Moderate	
8	cenegermin	Non-Onco	Adult	Yes	November 2017	Fully innovative	Important	Important	Low	
9	ceftazidime / avibactam	Non-Onco	Adult	No	July 2017	Not innovative	Important	Poor	Low	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
10	nivolumab	S	Adult	No	September 2017	Not innovative	Important	N/A	Low	*The added therapeutic value in this indication was considered not assessable*
11	allogeneic t cells genetically modified	H	Adult	Yes	September 2017	Not innovative	Moderate	Moderate	Very low	
12	daratumumab	H	Adult	Yes	October 2017	Fully innovative	Moderate	Important	Moderate	
13	sofosbuvir/ velpatasvir/ voxilaprevir	Non-Onco	Adult	No	July 2017	Fully innovative	Important	Important	Moderate	
14	adalimumab	Non-Onco	Adult	Yes	November 2017	Conditionally innovative	Important	Moderate	Moderate	
15	lenalidomide	H	Adult	Yes	September 2017	Conditionally innovative	Moderate	Moderate	Moderate	
16	inotuzumab ozagamicin	H	Adult	Yes	October 2017	Conditionally innovative	Moderate	Moderate	Moderate	
17	atezolizumab	S	Adult	No	November 2017	Fully innovative	Important	Moderate	High	
18	bezlotoxumab	Non-Onco	Adult	No	October 2017	Not innovative	Important	Moderate	Low	
19	dinutuximab beta	S	Mixed	Yes	February 2018	Fully innovative	Maximum	Important	Moderate	
20	dinutuximab beta	S	Mixed	Yes	February 2018	Not innovative	Maximum	Important	Very low	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
21	alectinib	S	Adult	No	January 2018	Conditionally innovative	Moderate	Moderate	Moderate	
22	alectinib	S	Adult	No	January 2018	Fully innovative	Moderate	Important	Moderate	
23	nivolumab	S	Adult	No	November 2017	Conditionally innovative	Important	Moderate	Moderate	
24	midostaurin	H	Adult	Yes	December 2017	Fully innovative	Moderate	Important	Moderate	
25	midostaurin	H	Adult	Yes	December 2017	Not innovative	Important	Poor	Low	
26	ibrutinib	H	Adult	Yes	October 2017	Conditionally innovative	Moderate	Moderate	Moderate	
27	dupilumab	Non-Onco	Adult	No	January 2018	Fully innovative	Important	Moderate	High	
28	ocrelizumab	Non-Onco	Adult	No	February 2018	Not innovative	Maximum	Poor	Moderate	
29	letermovir	Non-Onco	Adult	Yes	February 2018	Fully innovative	Moderate	Important	High	
30	avelumab	S	Adult	Yes	January 2018	Conditionally innovative	Important	Moderate	Low	
31	canakinumab	Non-Onco	Mixed	Yes	December 2017	Conditionally innovative	Important	Moderate	Moderate	
32	ibrutinib	H	Adult	Yes	July 2017	Not innovative	Poor	Poor	Moderate	
33	ribociclib	S	Adult	No	November 2017	Conditionally innovative	Moderate	Moderate	Moderate	
34	nivolumab	H	Adult	Yes	July 2017	Conditionally innovative	Maximum	Moderate	Low	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
35	niraparib	S	Adult	Yes	January 2018	Conditionally innovative	Important	Moderate	Moderate	
36	regorafenib	S	Adult	No	February 2018	Conditionally innovative	Maximum	Moderate	High	
37	emicizumab	Non-Onco	Mixed	Yes	June 2018	Fully innovative	Moderate	Important	Low	
38	ethyl telotristat	S	Adult	Yes	January 2018	Not innovative	Important	Poor	Moderate	
39	liposomal daunorubicin hydrochloride / cytarabine	H	Adult	Yes	November 2018	Fully innovative	Moderate	Important	Moderate	
40	pembrolizumab	S	Adult	No	May 2019	Fully innovative	Moderate	Important	High	
41	tocilizumab	Non-Onco	Adult	Yes	July 2018	Conditionally innovative	Moderate	Moderate	Moderate	
42	daratumumab	H	Adult	Yes	October 2017	Fully innovative	Moderate	Important	Moderate	
43	cladribine	Non-Onco	Adult	No	April 2018	Not innovative	Moderate	Poor	Very low	
44	lutetium oxodotreotide	S	Adult	Yes	March 2018	Fully innovative	Important	Important	Low	
45	darvadstrocel	Non-Onco	Adult	Yes	April 2019	Not innovative	Moderate	Poor	Low	
46	cysteamine	Non-Onco	Mixed	Yes	January 2018	Not innovative	Poor	Moderate	Very low	
47	obinutuzumab	H	Adult	Yes	March 2018	Not innovative	Poor	Poor	Moderate	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
48	pembrolizumab	S	Adult	No	June 2018	Conditionally innovative	Important	Moderate	High	
49	pembrolizumab	H	Adult	Yes	November 2017	Conditionally innovative	Maximum	Moderate	Low	
50	pertuzumab	S	Adult	No	November 2018	Not innovative	Moderate	Poor	Moderate	
51	tisagenlecleucel	H	Mixed	Yes	January 2019	Fully innovative	Important	Important	Moderate	
52	tisagenlecleucel	H	Adult	Yes	January 2019	Fully innovative	Important	Important	Low	
53	burosumab	Non-Onco	Pediatric	Yes	December 2018	Conditionally innovative	Important	Moderate	Low	
54	durvalumab	S	Adult	No	March 2019	Fully innovative	Important	Important	Moderate	
55	lenvatinib	S	Adult	Yes	April 2019	Not innovative	Important	Absent	Moderate	
56	brentuximab vedotin	H	Adult	Yes	April 2018	Conditionally innovative	Moderate	Moderate	Moderate	
57	pembrolizumab	S	Adult	No	May 2019	Fully innovative	Important	Moderate	High	
58	pembrolizumab	S	Adult	No	May 2019	Fully innovative	Moderate	Important	Moderate	
59	nivolumab	S	Adult	No	April 2019	Fully innovative	Important	Moderate	High	
60	osimertinib	S	Adult	No	February 2019	Fully innovative	Moderate	Important	Moderate	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
61	axicabtagene ciloleucel	H	Adult	Yes	January 2019	Fully innovative	Important	Important	Moderate	
62	dabrafenib	S	Adult	No	April 2019	Fully innovative	Important	Important	High	
63	trametinib	S	Adult	No	April 2019	Fully innovative	Important	Important	High	
64	doravirina/ lamivudina/ tenofovir disoproxil	Non-Onco	Adult	No	May 2019	Not innovative	Poor	Poor	Moderate	
65	doravirine	Non-Onco	Adult	No	May 2019	Not innovative	Poor	Poor	Moderate	
66	venetoclax	H	Adult	Yes	April 2019	Conditionally innovative	Moderate	Moderate	Moderate	
67	abemaciclib	S	Adult	No	May 2019	Conditionally innovative	Moderate	Moderate	Moderate	
68	caplacizumab	Non-Onco	Adult	Yes	February 2019	Conditionally innovative	Moderate	Moderate	Low	
69	patisiran	Non-Onco	Adult	Yes	November 2018	Fully innovative	Important	Important	Moderate	
70	emicizumab	Non-Onco	Mixed	Yes	October 2019	Conditionally innovative	Moderate	Moderate	Low	
71	metreleptin	Non-Onco	Mixed	Yes	February 2019	Conditionally innovative	Maximum	Moderate	Very low	*Ultra-rare disease*
72	abiraterone acetate	S	Adult	No	May 2018	Not innovative	Moderate	Poor	Moderate	
73	alirocumab	Non-Onco	Adult	No	November 2019	Not innovative	Moderate	Poor	Moderate	

ID	Medicine	Disease Group	Population	Rare disease*	CTS date	Innovation status	Unmet need	Added value	Quality of evidence	*Notes*
74	encorafenib	S	Adult	No	May 2019	Not innovative	Moderate	Poor	Moderate	
75	binimetinib	S	Adult	No	May 2019	Not innovative	Moderate	Poor	Moderate	
76	lanadelumab	Non-Onco	Mixed	Yes	December 2019	Not innovative	Moderate	Poor	Moderate	
77	cerliponase alfa	Non-Onco	Pediatric	Yes	December 2018	Fully innovative	Maximum	Important	Very low	*Ultra-rare disease*

** according to orphanet*

AIFA: italian medicines agency; CTS: techical-scientific commitee; H: hematological malignancies; S: solid tumor; onco: oncological disease; non-onco: non oncological disease

Supplementary Figure 1. Deterministic decision tree based on the available innovativeness appraisals released by the Italian Medicines Agency (2017-2020)