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RESEARCH

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Exploring the connection between EU-funded research and methodological approaches: insights from a retrospective analysis

Pierre Deceuninck[1], Annalisa Gastaldello[1*], Milena Mennecozzi[1] and Francesca Pistollato[2]

Abstract

Background Over the last two decades, substantial investments have been directed towards supporting fundamental and applied research in Alzheimer's disease (AD), breast cancer (BC), and prostate cancer (PC), which continue to pose significant health challenges. Recently, the Joint Research Centre (JRC) of the European Commission (EC) conducted a retrospective analysis to examine the major scientific advancements resulting from EU-funded research in these disease areas and their impact on society.

Methods Building upon this analysis, our subsequent investigation delves into the methodological approaches—both animal and non-animal models and methods—employed in AD, BC, and PC research funded under past EU framework programs (FP5, FP6, FP7, and H2020), and explored the notable research outputs associated with these approaches.

Results Our findings indicate a prevalent use of animal-based methodologies in AD research, particularly evident in projects funded under H2020. Notably, projects focused on drug development, testing, or repurposing heavily relied on animal models. Conversely, research aimed at clinical trial design, patient stratification, diagnosis and diagnostic tool development, lifestyle interventions, and prevention—outputs with potential societal impact—more frequently utilised non-animal methods. Advanced investigations leveraging imaging, computational tools, biomarker discovery and organ/tissue chip technologies predominantly favoured non-animal strategies.

Conclusions These insights highlight a correlation between methodological choices and the translational potential of research outcomes, suggesting the need for a reconsideration of research strategy planning in future framework programs.

Keywords Alzheimer's disease, Breast cancer, Prostate cancer, European Commission, Framework programme, Methods, Outputs, Societal impact, Innovation, Funding, Indicators

Introduction

Non-communicable diseases (NCD)s contribute to 90% of all deaths within the European Union (EU) [1]. These diseases also incur the highest healthcare expenses, amounting to 115 billion Euro annually, equivalent to 0.8% of GDP, along with additional societal costs such as productivity loss and workforce reduction [2]. Despite notable research achievements, the prevalence of major

*Correspondence:
Annalisa Gastaldello
Annalisa.GASTALDELLO@ec.europa.eu
[1] European Commission, Joint Research Centre (JRC), Ispra, Italy
[2] Humane Society International, Avenue Des Arts 50, 1000 Brussels, Belgium

NCDs, like dementia and cancer, has shown no decline over time [3, 4]. Within the realm of NCDs, dementia is projected to affect 78 million people globally by 2030, escalating to 139 million by 2050 [5]. Notably, Alzheimer's disease (AD) remains the most prevalent and burdensome form of dementia, representing an unmet medical need (UMN) due to its incurable nature. While prognosis for AD onset can be somewhat predicted, currently available treatments have shown limited efficacy in halting the neurodegenerative process that exacerbates symptoms [6, 7].

Among cancers, breast cancer (BC) stands out as the predominant form of cancer among women, with considerable prevalence and incidence across the EU [8].

On the other hand, prostate cancer (PC) ranks as the most prevalent malignancy among males, particularly affecting those in their fifth, sixth, seventh, and eighth decades of life [9].

Over the last twenty years, the European Commission (EC) has consistently supported research projects focused on AD, BC, and PC through four successive funding cycles: Framework Programmes FP5, FP6, FP7, and Horizon 2020 (H2020). Recent retrospective analyses conducted by the Joint Research Centre (JRC) of the EC [10–12], aimed to assess by means of refined indicators: (i) the level of productivity and innovation achieved in these funded projects; (ii) the extent to which outputs from EU-funded biomedical research projects translated into tangible societal impacts; and (iii) the factors contributing to research success and impact. Societal impact refers to the influence or benefits of research that extend beyond academia, affecting e.g., health, economy, society, public policy or services, and the environment, ultimately enhancing the quality of life.

A 2023 technical report from the JRC [12, 13] and a very recent peer-reviewed article summarised the most relevant takeaways of this study [14], showing that although BC research received comparatively less funding than AD research, BC-focused projects, particularly those funded under FP7 and H2020, yielded a notably higher number of scientific breakthroughs with potential implications for public health. These breakthroughs included the development of diagnostic tools, treatments, medical devices, new drugs, and preventive measures. Additionally, prior retrospective analyses conducted by the JRC through surveys and interviews with funding recipients in these three research areas [10, 11] indicated that projects emphasizing human-centred research strategies generally tend to have more immediate societal impact.

In a more recent analysis [15], we investigated the correlation between methodological approach selection—specifically, the use of animal versus non-animal methods, including human-based models and in silico approaches—and the generation of key scientific outputs within the analysed projects. Additionally, we examined the volume of scientific articles published as part of these research endeavours.

Here we report the most relevant outcomes of this extensive analysis and discuss their broader implications, considering global health trends. Collectively, these retrospective evaluations enabled us to pinpoint both highly impactful and less impactful research endeavors and funding channels. These findings emphasise the connection between methodological approaches and research outputs with translational potential, emphasising the need for a reassessment of research strategy planning within current and forthcoming framework programs.

Methodological approach

Biomedical research areas, EU funding, geographical scope and indicators

AD, BC and PC related projects funded through FP5, FP6, FP7 and H2020 spanning 21 years (from 1st of January 1999, until 31st of December 2019) were analysed. To narrow the scope of this analysis, only projects that received more than 200 K Euro funding were analysed, for a total of 590 projects and a volume of 2,8 billion Euro, covering around 90% of total EU funding allocated on these three areas of research. While several types of dementia and cancer exist, these research areas were selected based on their high prevalence in the European morbidity landscape. The analysis focused on EU-funded biomedical research granted to beneficiaries from EU Member States (MS) and other eligible consortia partners, and considered also the United Kingdom, since it had been a member of the EU for the reference period.

A final list of 14 refined indicators clustered into six categories (i.e., funding/economic; dissemination; scientific/technological; regulatory and policy; public health trends; education, training, and job opportunities) (see Table A in [15]) was used to analyse EC-funded AD, BC, and PC research across the four analysed framework programmes.

Major research outputs and publications in relation to the EU framework programmes, research areas and methodological approaches

A 'major research output' encompassed any scientific or technological outcome, i.e., 'model/method development, molecular mechanisms and/or disease mechanisms' (categorised as "basic/applied research" related projects), 'patents', 'diagnosis','diagnostic tools', 'drug development, testing and/or repurposing', 'drugs, treatments and/or medical devices', 'clinical trials', 'patient stratification', 'life-style and/or, prevention', 'nutrition',

'imaging', 'biomarkers', 'computational', 'chip' (organ or tissue chip), and 'nano-technologies'.

Furthermore, among dissemination outputs, the number of publications were considered. Additionally, the analysis examined whether the methodologies described in the projects were based on animal or non-animal approaches (human-based in vitro models, human samples, human cohorts, or in silico methods, or a combination thereof). The entire dataset is freely accessible and stored in the JRC Data Catalogue [13]. Data analysis was conducted using the free software R analytics (https://www.r-project.org/), and customised scripts were developed to perform a systematic quantitative and cross-dimensional analysis of the data. More details about this analysis are reported in [15].

Results

Number of projects

Animals and non-animal approaches in research projects across different funding programmes

Across all four programs (FP5, FP6, FP7, and H2020), our analysis revealed that, on average, 60% of projects (352 in total) did not involve the use of animals and instead relied on human-based models or materials, or utilised in silico technologies (Fig. 1). This percentage was slightly higher for PC and BC research compared to AD research (67%, 61%, and 55% respectively), and for FP5, FP6, and FP7 compared to H2020 (69%, 68%, 62%, and 50% respectively). The proportion of PC projects relying on animals increased over time, while this percentage remained

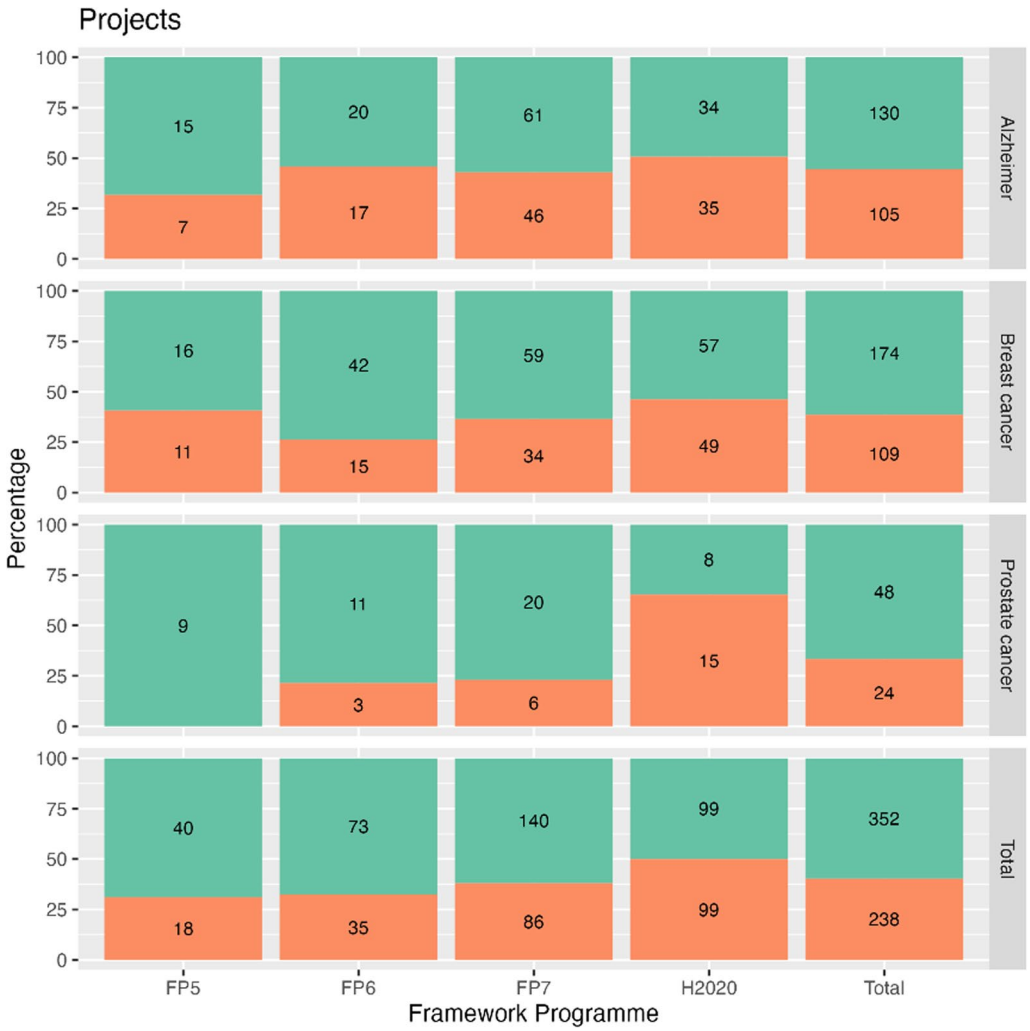

Fig. 1 Numbers and relative percentages of AD, BC and PC projects across framework programmes (FP5, FP6, FP7 and H2020) that accounted for the use of animals alone or in combination with other non-animal methods (orange bars) or based exclusively on non-animal methods and technologies (green bars). Y axis reports percentage values, whilst absolute project numbers are reported inside bars

relatively stable across the framework programs for AD and BC research (Fig. 1).

Basic and applied research projects

Upon analysing various categories of research outputs and applications, we found that 56% of projects (329 out of 590) focused on basic and applied research activities. These activities delved into molecular or disease mechanisms, or were involved in developing new models or methods.

Interestingly, animals were utilised in nearly half of these projects in each disease area and across framework programs, except for H2020 where animal projects constituted the majority (61%) (Fig. 2). Conversely, the use of non-animal approaches within this research output category was higher in BC and PC projects compared to AD projects (55%, 56%, and 46% respectively) and across older framework programs (56%, 55%, 57%, and 39% for FP5, FP6, FP7, and H2020 respectively) (Fig. 2). When considering animal use across areas and FPs, the percentage of both AD and PC projects that relied on animals increased over time, while it remained stable across FPs for BC research (Fig. 2).

Projects with patents

When examining patents as an output category, we observed that no patents were obtained within the context of FP5 and FP6, whist under FP7 and H2020, a total

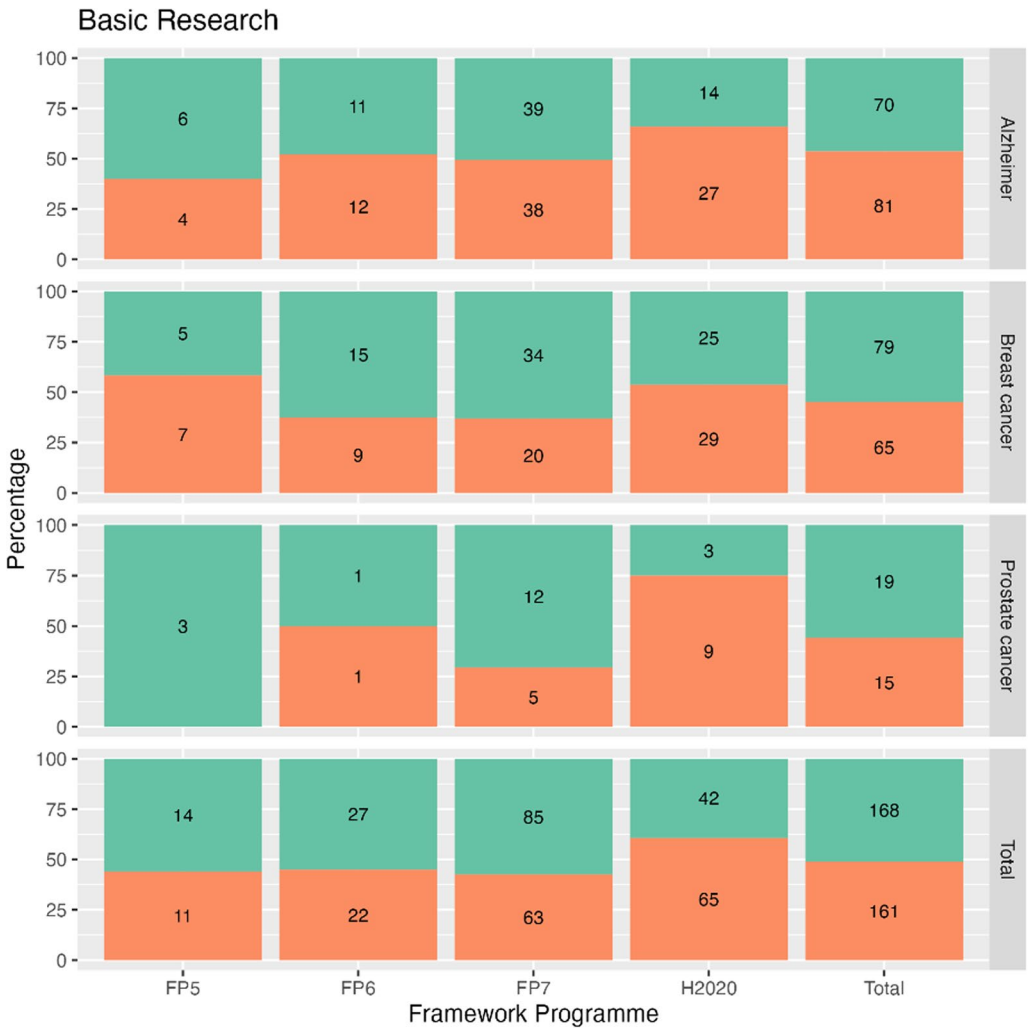

Fig. 2 Numbers and relative percentages of AD, BC and PC basic/applied research projects across framework programmes (FP5, FP6, FP7 and H2020) that accounted for the use of animals alone or in combination with other non-animal methods (orange bars) or based exclusively on non-animal methods and technologies (green bars). Y axis reports percentage values, whilst absolute project numbers are reported inside bars

of 60 projects resulted in the filing of at least one patent. Regarding the methodological approach, 50% of AD projects that obtained patent(s) (11 out of 22) involved the use of animals, whereas this proportion was slightly lower for cancer-related projects (40% for BC and 38% for PC). Of note, the percentage of AD projects that filed patents and relied exclusively on non-animal approaches increased in H2020 compared to FP7 (Fig. 3).

Projects focused on diagnostic tools or diagnosis

On average, 41% of projects across all research areas and programs (242 out of 590 projects) were dedicated to designing diagnostic tools. Across all these projects, a minority utilised animal models (26%). The proportions of projects dedicated to non-animal approaches were similar across the three research areas, with some differences observed across framework programs. The use of animals underwent a modest increase over time (Fig. 4A).

Similarly, 17% of projects (100 out of 590) addressed diagnosis as their main topic (Fig. 4B). A significant percentage of projects in this category utilised non-animal models, with 85%, 89%, and 76% of AD, BC, and PC projects falling into this category, respectively. Notably, none of the eight FP5 projects involved animal use.

Projects on drug development, treatment or repurposing, and/or the creation of a medical device

Another output category with significant potential societal impact involves drug development, drug treatment, or the creation of medical devices. Overall, 61% of these

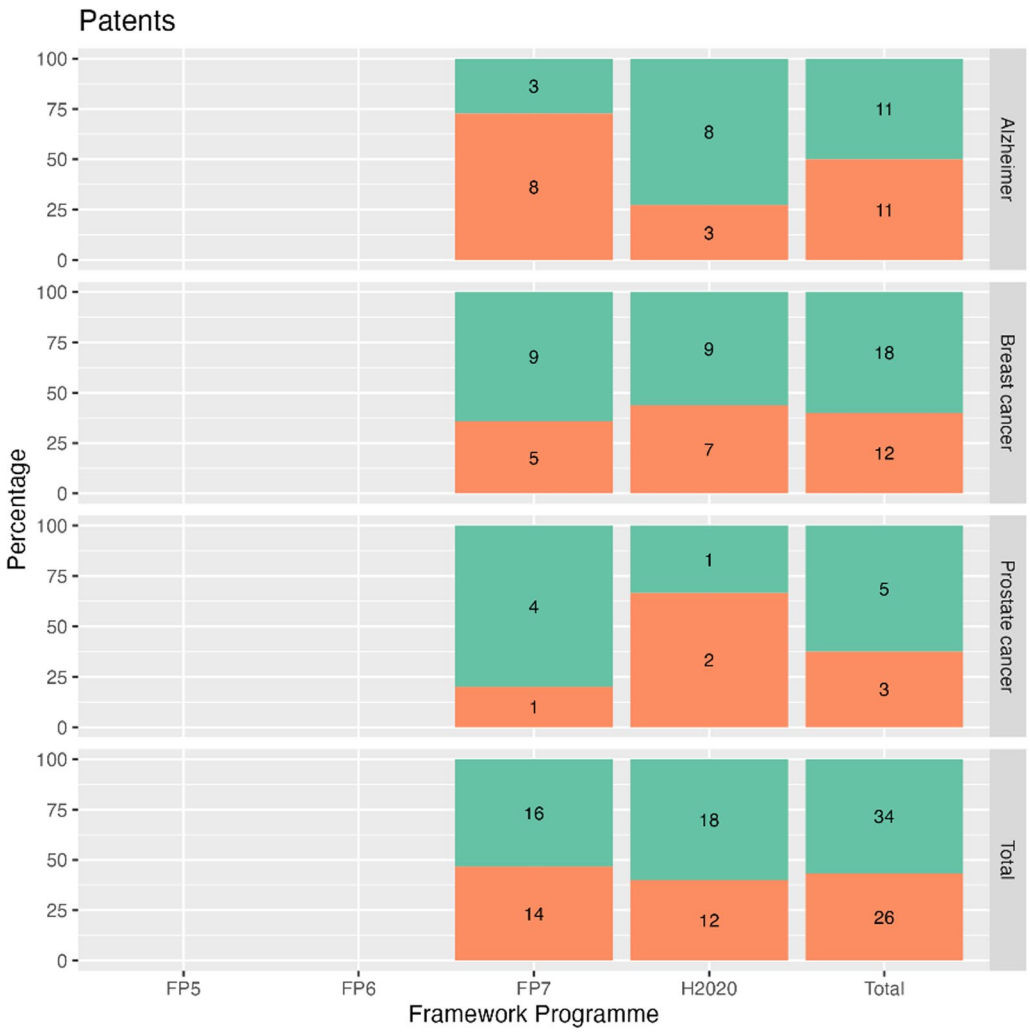

Fig. 3 Numbers and relative percentages of AD, BC and PC projects that filed patents across framework programmes (FP5, FP6, FP7 and H2020) that accounted for the use of animals alone or in combination with other non-animal methods (orange bars) or based exclusively on non-animal methods and technologies (green bars). Y axis reports percentage values, whilst absolute project numbers are reported inside bars

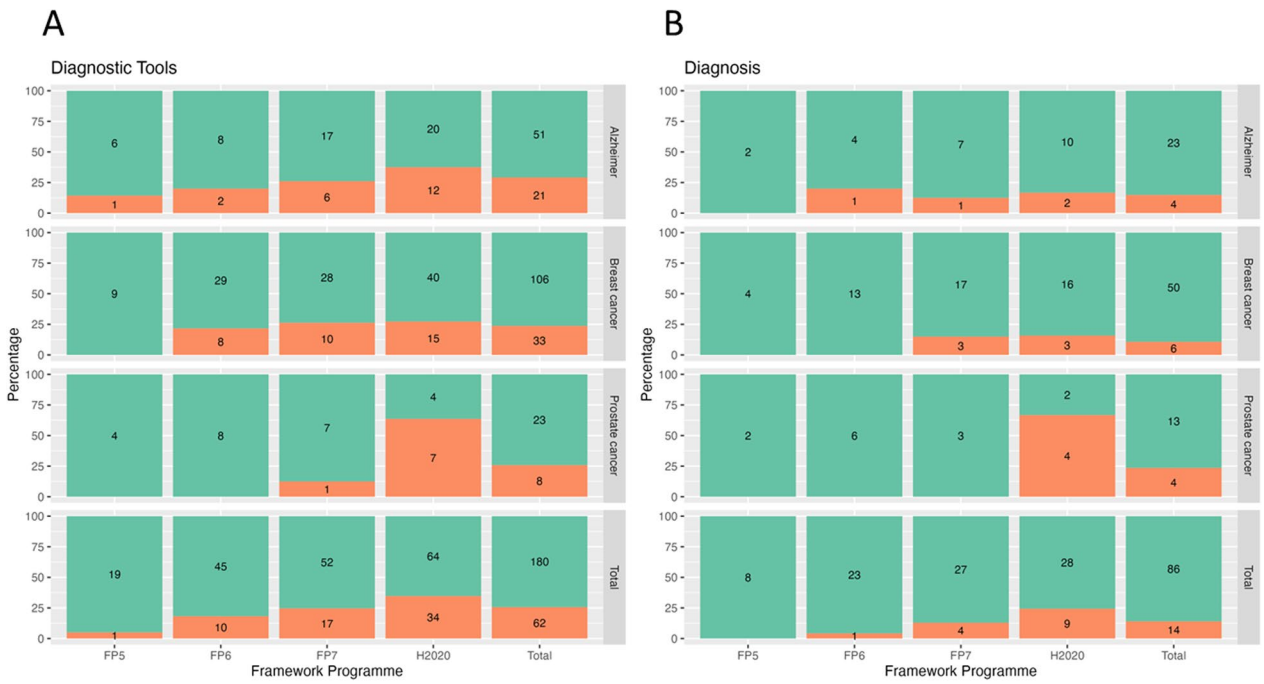

Fig. 4 Numbers and relative percentages of AD, BC and PC projects that focused on diagnostic tool development (**A**) and addressed diagnosis (**B**) across framework programmes (FP5, FP6, FP7 and H2020) that accounted for the use of animals alone or in combination with other non-animal methods (orange bars) or based exclusively on non-animal methods and technologies (green bars). Y axis reports percentage values, whilst absolute project numbers are reported inside bars

projects did not incorporate animal approaches; this proportion was slightly higher for AD research (66%) compared to BC and PC research (58% and 59%, respectively), and for FP5 and FP7 (72% and 67%, respectively) compared to FP6 and H2020 (59% and 55%, respectively) (Fig. 5A). The distribution of percentages over time for AD and BC projects under this output category, comparing those that utilised animals versus those that did not, remained relatively stable, while a tendency towards an increase in animal usage was observed in PC research (Fig. 5A).

Upon closer examination, we delved into projects specifically focused on the development, repurposing, or testing of drugs, revealing that only 11% of the total projects (64 out of 590) centred on these applications (Fig. 5B). Interestingly, 57%, 77%, and 45% of AD, BC and PC projects, respectively, falling under this output category, utilised animal models (averaging at 64%) (Fig. 5B). High proportions of projects considering the use of animals were observed for FP6 (77%) and H2020 (78%) (Fig. 5B).

Projects on clinical trial design and patient stratification

Roughly one out of every five projects, on average, focused on clinical trials, comprising 119 out of a total of 590 projects. The percentage of projects abstaining from using animal models was notably higher, averaging at 68%, compared to those considering animal usage, which averaged at 32% (Fig. 6A). Particularly, the proportion of all PC projects employing non-animal methods was higher (76%), compared to AD (62%) and BC (69%) projects. Comparing the funding programs, H2020 supported 72% of non-animal approach projects, surpassing earlier programs (Fig. 6A). Noteworthy, non-animal methods were predominant in AD projects involving clinical trials under the most recent framework program (H2020), this proportion remained stable for BC projects, whilst it showed a decreasing trend for PC projects (although only two PC projects addressed clinical trials under H2020, one of which accounted for animals the other did not) (Fig. 6A).

Only 20 in 590 projects (3%) integrated patient stratification into their strategies. Notably, within this output category, the predominant approach was the utilisation of non-animal methods, with 80%, 92%, and 100% of AD, BC and PC projects, respectively, abstaining from animal use (Fig. 6B). This pattern persisted across different funding cycles, with all projects from FP6 and FP7, and the majority from FP5 and H2020 (80% and 88%, respectively), relying solely on non-animal methodologies (Fig. 6B).

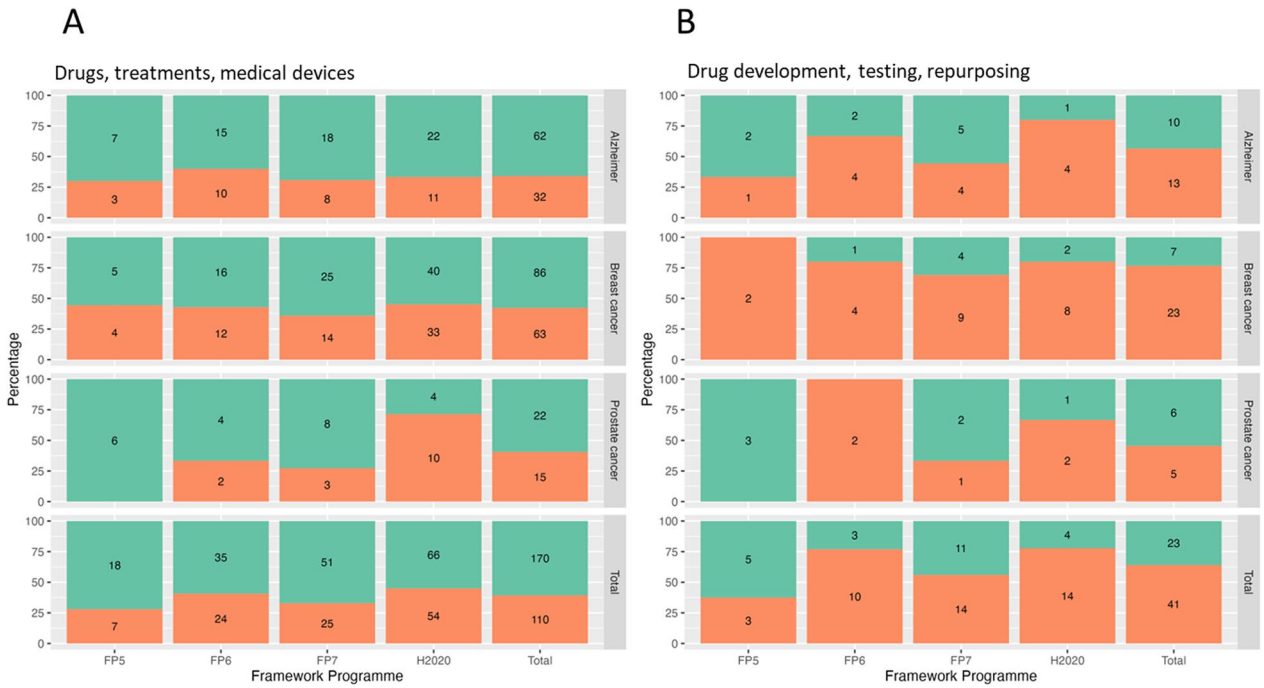

Fig. 5 Numbers and relative percentages of AD, BC and PC projects that focused on drugs, treatments or medical devices (**A**) or on drug development, testing or repurposing (**B**), across framework programmes (FP5, FP6, FP7 and H2020) that accounted for the use of animals alone or in combination with other non-animal methods (orange bars) or based exclusively on non-animal methods and technologies (green bars). Y axis reports percentage values, whilst absolute project numbers are reported inside bars

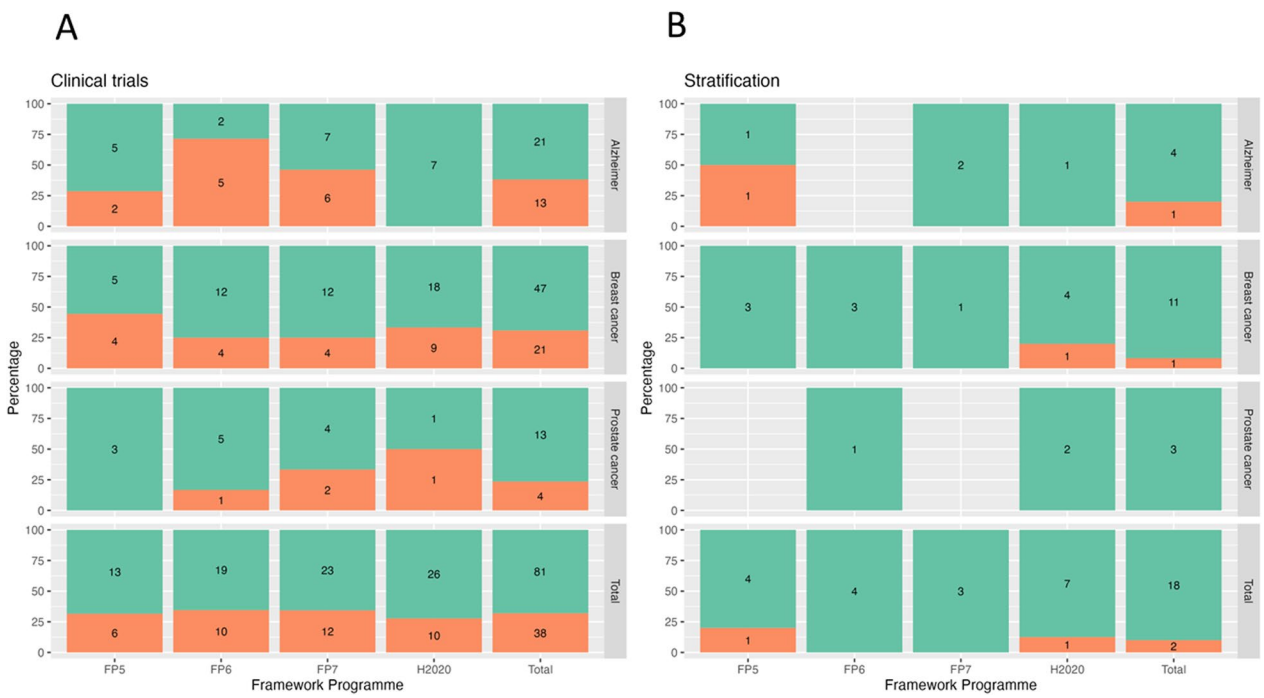

Fig. 6 Numbers and relative percentages of AD, BC and PC projects with clinical trials (**A**) and patients stratification (**B**) across framework programmes (FP5, FP6, FP7 and H2020) that accounted for the use of animals alone or in combination with other non-animal methods (orange bars) or based exclusively on non-animal methods and technologies (green bars). Y axis reports percentage values, whilst absolute project numbers are reported inside bars

Projects on lifestyle, prevention or nutrition-related topics

Within the spectrum of outputs potentially affecting society, we also examined projects concentrating on lifestyle or prevention research. Despite AD, BC and PC being NCDs, where the risk of onset can be mitigated through lifestyle-based interventions [16–19], only 8% of the projects scrutiniszed (45 out of 590) in this analysis delved into lifestyle or prevention-related subjects (Supplementary Fig. 1A).

The majority of these projects eschewed the use of animal models in their research strategies, with 79% of AD projects, 73% of BC projects and 100% of PC projects following suit, alongside 71% for FP5, 85% for FP6, 75% for FP7, and 76% for H2020. It is worth noting that under H2020, no PC projects were dedicated to lifestyle or prevention-related topics (Supplementary Fig. 1A).

Similarly, the percentage of projects specifically targeting nutrients or nutrition-related research topics was exceedingly low, with only 3 out of 590 projects (less than 1%). Notably, none of these projects encompassed PC research. When considering the selected methodologies, 2 of these 3 projects involved the utilisation of animals in their research strategies (Supplementary Fig. 1B).

Projects that considered other outputs with potential for future impact

We conducted a further assessment of projects focusing on the development or application of technologies involving imaging technologies, biomarker discovery, computational approaches, chip technologies (such as organ/tissue-on-a-chip), and nano-technologies. A total of 61 out of 590 projects incorporates these technologies (10%) (Supplementary Fig. 2).

Specifically, the proportion of projects concentrating on imaging-related applications was 4% (21 out of 590 projects), and about one-third involved the use of animals, with a lower proportion observed for AD projects (17%), and higher proportions for BC (30%) and PC projects (60%). No projects considering these technologies received funding during FP5, only one was funded in FP6, while 11 and 9 projects were funded under FP7 and H2020, respectively. H2020 stood out as the sole program where the majority of projects were animal-based (5 out of 9 projects) (Supplementary Fig. 2A).

When evaluating projects that delved into biomarker discovery, similar observations emerged: these projects constituted a minuscule fraction of the overall EU budget (2% of projects, totalling 10 out of 590). Animals were utilised in 2 out of 3 PC projects, while projects focusing on AD and BC employed non-animal methods (Supplementary Fig. 2B). No projects on biomarkers received funding during the earliest programs (FP5 and FP6), while during the most recent ones (FP7 and H2020), 8 and 2 projects were funded respectively. The majority of projects during FP7 utilised non-animal approaches (7 out of 8), whereas during H2020, one project involved animal usage, and one did not (Supplementary Fig. 2B).

Similarly, only 1% of total projects (8 out of 590) focused on computer-based applications, and all of them relied on non-animal methodologies (Supplementary Fig. 2C).

Likewise, only 4 AD projects considered the utilization of (organ/tissue) chip technologies, with three of them adopting non-animal approach methodologies (Supplementary Fig. 2D).

Nanotechnologies were addressed in 18 projects (3% of total), and none of these were funded during the earliest programs (FP5 and FP6). Additionally, while 60% of projects during FP7 were non-animal based, all projects funded during the latest program (8 in H2020) involved animal usage (Supplementary Fig. 2E).

Peer-reviewed articles

Number of articles published in the contest of AD, BC and PC projects that consider the use of animals or non-animal methods

We further examined the utilisation of animals versus non-animal approaches in articles pertaining to AD, BC and PC research projects, while considering the different scientific outputs investigated in the previous sections. On average, 53% of articles (6611 out of 12,591) referenced animal models either alone or in conjunction with other non-animal methods, with this percentage being higher for AD (55%) and BC (52%), and lower for PC (39%) (Fig. 7). Notably, 24% of the 12,591 articles analysed exclusively relied on animal models without incorporating other human in vitro or in silico tools (24% of AD, 28% of BC, and 11% of PC related articles) (see Table 12 in [15]).

When examining the percentages of articles with or without animal usage across different areas and framework programs, we observed a slight upward trend over time in the percentage of AD articles involving animal use (Fig. 7). Similarly, the percentage of PC articles incorporating animal research exhibited a noteworthy increase under H2020 compared to FP6 and FP7, while the percentage of BC articles experienced a decline since FP5 (Fig. 7).

Basic and applied research-related articles

We observed that 62% of the articles (7746 out of 12,591) centred on basic and applied research activities, investigating molecular or disease mechanisms, or working on the development of new models or methods. Overall, 59% of these articles utilised animals. When examining the percentage distribution across different areas and

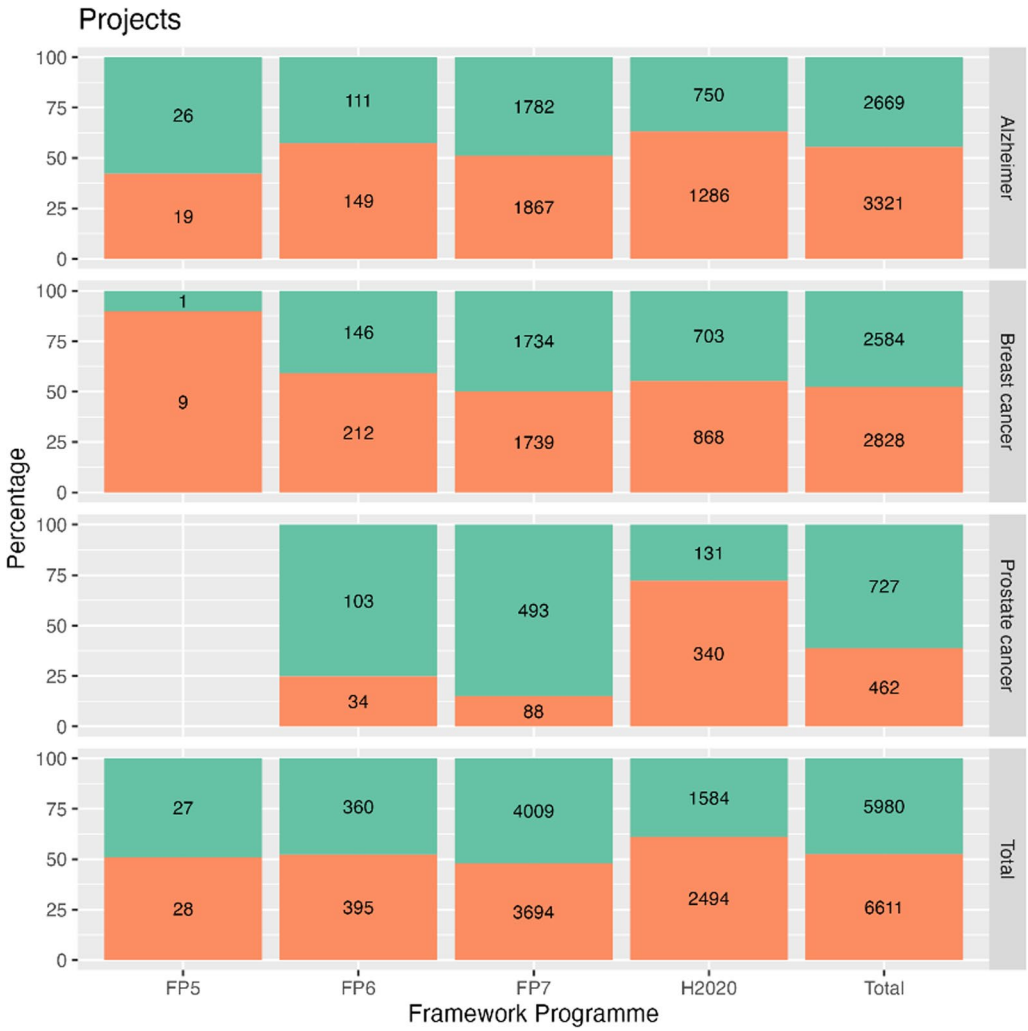

Fig. 7 Numbers and relative percentages of papers from projects on AD, BC and PC across framework programmes (FP5, FP6, FP7 and H2020) that accounted for the use of animals alone or in combination with other non-animal methods (orange bars) or based exclusively on non-animal methods and technologies (green bars). Y axis reports percentage values, whilst absolute numbers of papers are reported inside bars

framework programs, we primarily observed an uptick in the proportion of PC articles involving animal studies in H2020 compared to FP7 (Fig. 8).

Articles published in the context of projects with one or more patents

An overall 19% of articles (2376 out 12,591 total) were published within the FP7 and H2020 projects that led to the filing of at least one patent; on average, 71% of these articles (1696 out of 2376) were associated with research activities utilising animals (74% on AD, 75% on BC, and 42% on PC) (Fig. 9).

The overall percentage of articles linked to non-animal-based projects with at least one patent increased in H2020 (39%) compared to FP7 (25%). However, these articles primarily focused on BC research, while the percentage of PC articles incorporating animal experiments followed an opposite (increasing) trend (Fig. 9).

Articles focused on diagnostic tools and diagnosis applications

Almost 50% of the articles (6292 out of 12,591 total) were published within the context of projects mentioning diagnostic tools, with 54% of them on average relying on non-animal methods (66% of PC, 61% of AD, and 47% of BC related articles) (Fig. 10A).

The percentage of articles from projects mentioning diagnostic tools and not utilising animals decreased in H2020 (50% in H2020 versus 64% in FP6) (Fig. 10A), particularly notable when considering the percentages

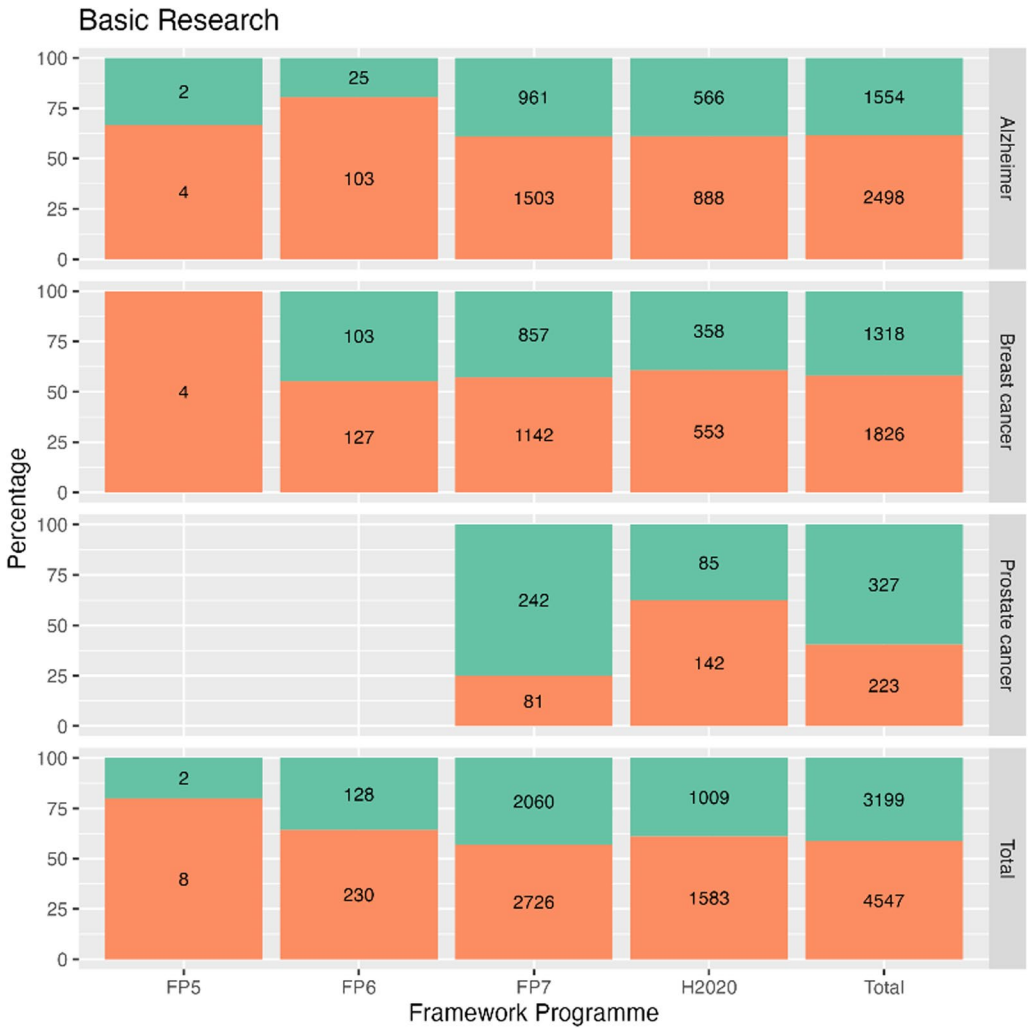

Fig. 8 Numbers and relative percentages of papers from projects on AD, BC and PC focused on basic/applied research across framework programmes (FP5, FP6, FP7 and H2020) that accounted for the use of animals alone or in combination with other non-animal methods (orange bars) or based exclusively on non-animal methods and technologies (green bars). Y axis reports percentage values, whilst absolute numbers of papers are reported inside bars

of PC articles (19%), i.e., only 46 out of 247 PC-related articles did not consider the use of animals. Conversely, an opposite trend was noted for BC articles not utilising animals published during H2020, showing a higher percentage compared to FP7 and FP6 (Fig. 10A).

The overall percentage of articles within projects addressing diagnosis was 12% (1508 articles out of 12,591); 66% of these (1000 out of 1508) did not involve animals, with this percentage being higher in AD research (81%) (Fig. 10B). Articles published within AD, BC, and PC projects addressing diagnosis and involving the use of animals increased in H2020 (56%) compared to FP7 (26%) (Fig. 10B).

Articles focused on drug development, treatment or repurposing, and/or the creation of a medical device

In total, 39% of articles (4862 out of 12,591 total) were published within projects mentioning drug development, drug treatment, or the creation of a medical device, with 52% of them associated with animal research (Fig. 11A). This percentage was higher during FP6 (78%), with 592 out of 755 articles published under this framework programme, and on average 63% of these articles involved the use animals (81% of AD, 59% of BC, and 42% of PC articles under FP6) (Fig. 11A). Additionally, a notable increase in the percentage of PC papers under this category involving animal research was noted in H2020 funding program (Fig. 11A).

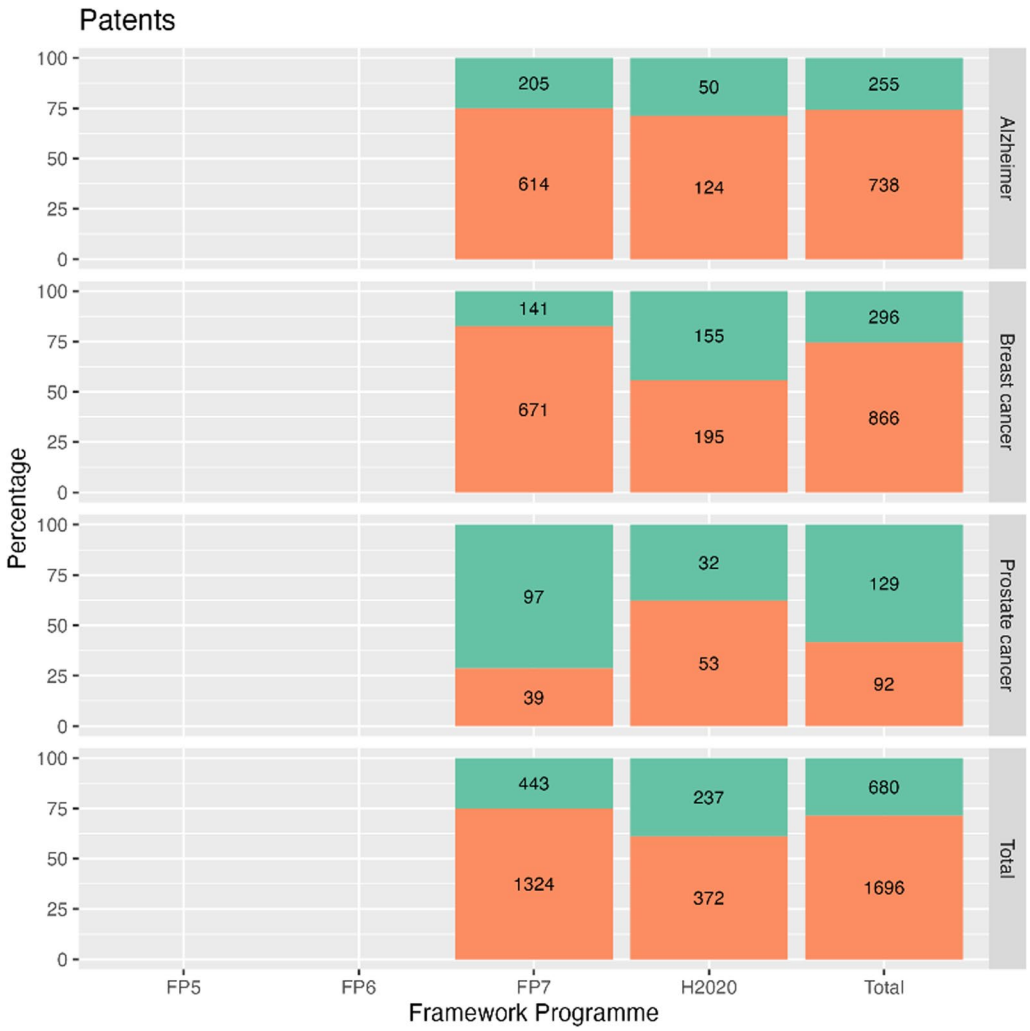

Fig. 9 Numbers and relative percentages of papers from projects on AD, BC and PC that filed patents across framework programmes (FP5, FP6, FP7 and H2020) that accounted for the use of animals alone or in combination with other non-animal methods (orange bars) or based exclusively on non-animal methods and technologies (green bars). Y axis reports percentage values, whilst absolute numbers of papers are reported inside bars

Furthermore, 9% of articles (1146 out of 12,591 total) were published within projects specifically focusing on the development, repurposing, or testing of drugs, with 85% of them addressing research involving animals (Fig. 11B). The overall percentages of articles from FP6, FP7 and H2020 projects involving animal research were 91%, 85% and 86%, respectively (Fig. 11B). Remarkably, under H2020, all AD and PC papers involved animal research (Fig. 11B).

Articles from projects focused on clinical trial design and patient stratification

Only 17% of articles (2174 out of 12,591 total) were published within the context of projects mentioning clinical trials. On average, 52% of these articles were associated with projects utilising animals (60% of AD, 48% of PC, and 45% of BC related articles) (Fig. 12A).

When examining percentage distributions considering animal versus non-animal use, it was found that while no AD articles involving animal research were published under H2020, for PC research, the trend was opposite, with all 55 papers (100%) published under H2020 involving animal experimentation. Regarding BC research, an increasing trend in the percentage of non-animal studies was observed since FP6 (Fig. 12A).

Only 4% (556 out of 12,591) of the articles were linked to projects focused on patient stratification, and most of the articles were published in the context of AD research. As expected considering the topic, the vast

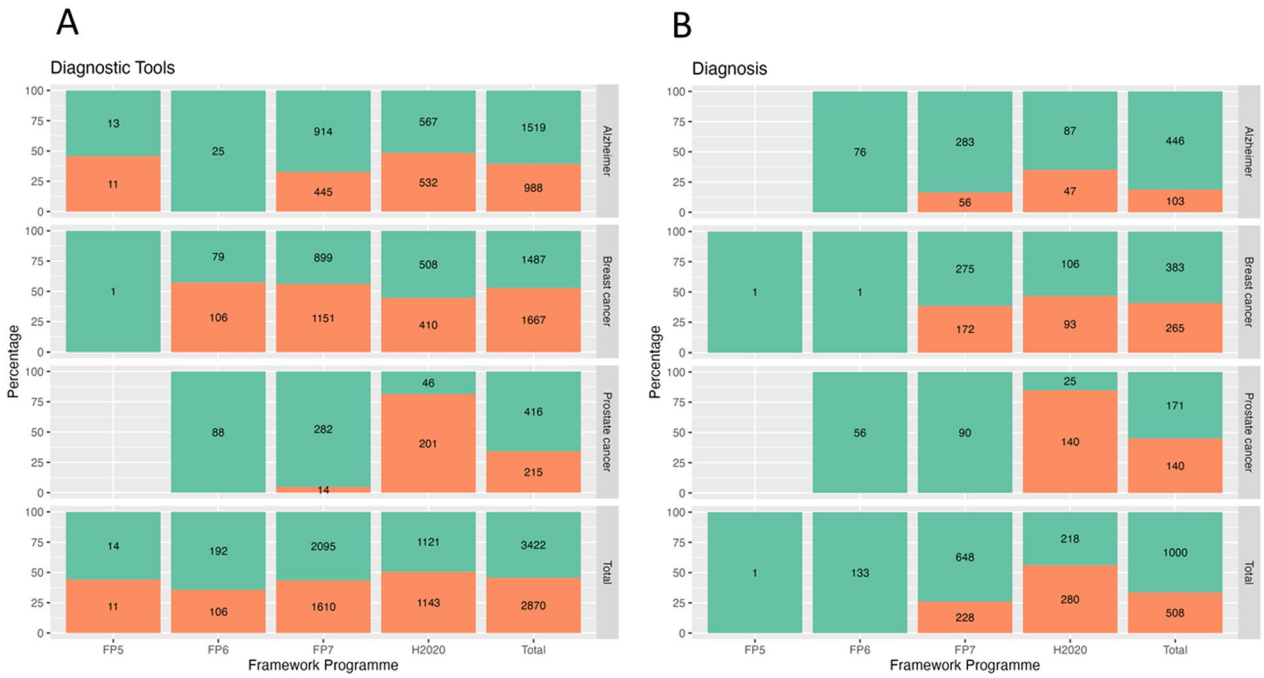

Fig. 10 Numbers and relative percentages of papers from projects on AD, BC and PC that focused on the development of diagnostic tools (**A**) and addressed diagnosis (**B**) across framework programmes (FP5, FP6, FP7 and H2020) that accounted for the use of animals alone or in combination with other non-animal methods (orange bars) or based exclusively on non-animal methods and technologies (green bars). Y axis reports percentage values, whilst absolute numbers of papers are reported inside bars

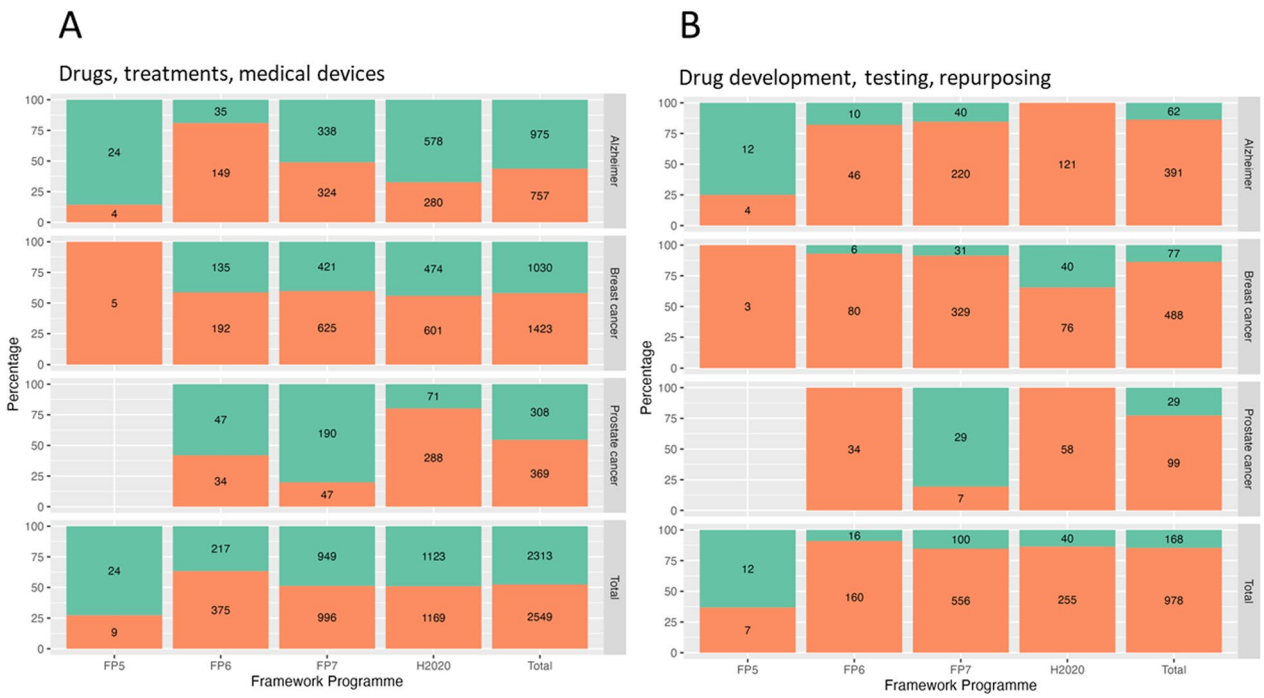

Fig. 11 Numbers and relative percentages of papers from projects on AD, BC and PC that focused on drugs, treatments or the creation of medical devices (**A**) or drug development, testing or repurposing (**B**) across framework programmes (FP5, FP6, FP7 and H2020) that accounted for the use of animals alone or in combination with other non-animal methods (orange bars) or based exclusively on non-animal methods and technologies (green bars). Y axis reports percentage values, whilst absolute numbers of papers are reported inside bars

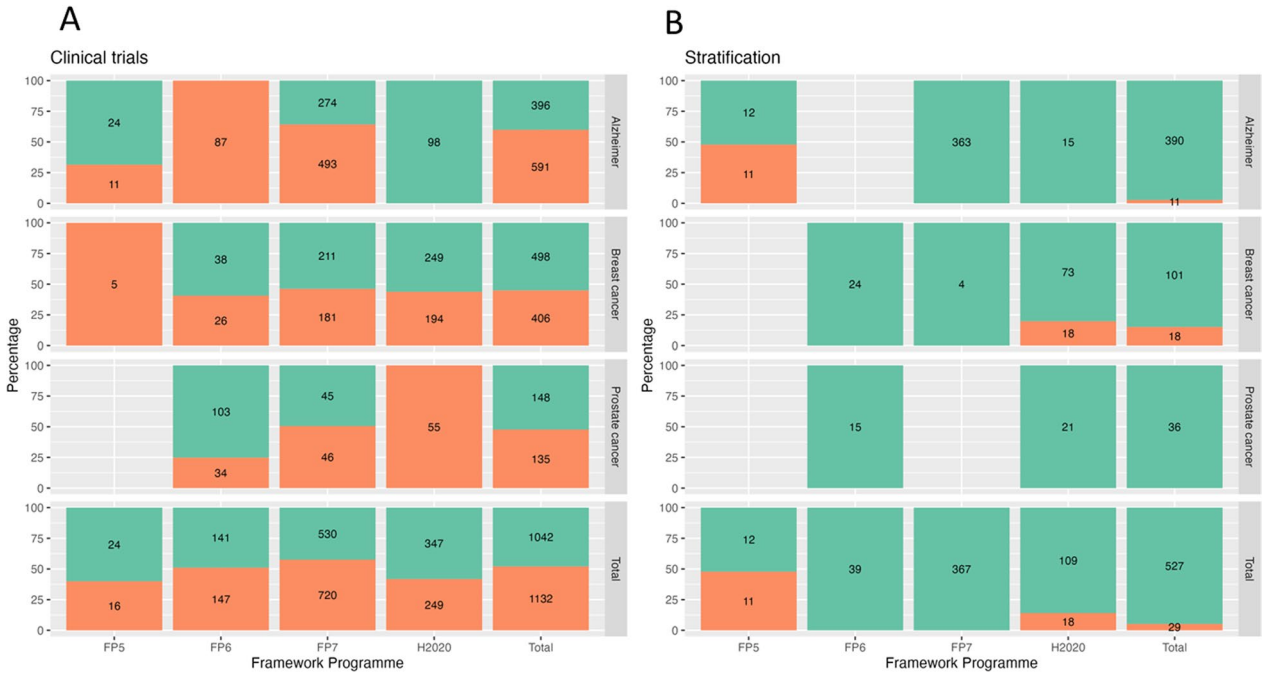

Fig. 12 Numbers and relative percentages of papers from projects on AD, BC and PC with clinical trials (**A**) and that considered patient stratification (**B**) across framework programmes (FP5, FP6, FP7 and H2020) that accounted for the use of animals alone or in combination with other non-animal methods (orange bars) or based exclusively on non-animal methods and technologies (green bars). Y axis reports percentage values, whilst absolute numbers of papers are reported inside bars

majority (95%) of these articles did not address the use of animals (Fig. 12B).

Articles from research activities focused on lifestyle, prevention or nutrition-related topics

Only 8% of articles (965 out of 12,591) were published within the context of research projects focusing on lifestyle and prevention, with 88% of them not involving animals, particularly evident in BC and PC research (Supplementary Fig. 3A). No articles on these topics were published during FP5. In addition, no PC research papers addressing lifestyle or prevention were published under H2020 Supplementary Fig. 3A).

Furthermore, the percentage of articles from projects specifically addressing nutrients or nutrition-related research was very low (less than 1%, 88 out of 12,591 articles); 85 focused on AD research (funded under FP7), 3 on BC research (funded under H2020), and all refer to animal methods (Supplementary Fig. 3B).

Articles from projects that considered other outputs with potential for future impact

Three percent of published papers (401 out of 12,591 total) were associated with activities focused on imaging-related applications. On average, 75% of these articles did not consider the use of animal methods, with a higher percentage observed for AD research (98%) compared to BC and PC research (76% and 61%, respectively) (Supplementary Fig. 4A). When examining the distribution of these articles across framework programs, no papers on these outputs were published under FP5 and FP6. A notable decrease in the percentage of articles from non-animal research focused on imaging was observed under H2020 (40%) compared to FP7 (89%) (Supplementary Fig. 4A), with these primarily being articles focused on PC research.

Furthermore, only 2% of articles (261 out of 12,591 total) were associated with projects focused on biomarkers, and 87% of them did not involve animals. Notably, no articles on biomarker research were published under older funding programs (FP5 and FP6). The only papers under this output category published under H2020 were those on PC research, and all of them involved animal experimentation in their methodological approach (Supplementary Fig. 4B).

Similarly, less than 2% of the articles (203 out of 12,591) published in the context of projects funded under FP7 and H2020 focused on computer-based applications, and none of them was associated with research involving animals (Supplementary Fig. 4C).

Likewise, only 223 articles (all in the area of AD, and mostly under FP7) focused on the development of chip

technologies. Under FP7, 79% of them involved the use of animals, while all 19 AD articles published under H2020 on this topic did not involve the use of animals (Supplementary Fig. 4D).

Finally, less than 3% of the articles (373 out of 12,591 total) focused on nanotechnologies. On average, 82% of them were based on research activities that involved the use of animals (especially for BC research, i.e., 87%) (Supplementary Fig. 4E). Remarkably, no paper on this topic was published under FP5 and FP6, and most of the published articles are associated with research projects funded under FP7. All the 72 articles within H2020 projects (69 on BC and 3 on PC) that focused on these technologies involved the use of animal models (Supplementary Fig. 4E).

Discussion

Measuring societal impact of funded research by looking at global health trends and other indicators

AD remains so far, an incurable disease; in 2019, the incidence of AD and other dementias in Europe was approximately 188/100,000, and between 1999 to 2019 (which covers the time interval considered in our analysis), the incidence of AD has even increased [20].

According to the EC estimates published in the European Cancer Information System (ECIS), BC remains the most diagnosed cancer in the EU, with an estimated 380,000 cases (about 13.8% of all cancer diagnoses). This is followed by colorectal (356,000; 13% of all new cases), PC (330,000; 12.1%), and lung cancer (319,000; 11.6%).

Correlating funded research with global health trends, such as mortality and incidence, is one way to measure the health gains derived from research efforts, or in other words, the return on investment derived from funded research. However, simply measuring health gains may not be representative of the overall impact of research, considering the other possible "spillovers" derived from research funding. For instance, bringing new medicines, medical devices and new technologies into healthcare, as well as contributing to the creation of new job opportunities, represent other outcomes with social impact [21]. In general, measuring societal impact is a complex task due to the lack of a standardised framework and the lack of reliable indicators [22–25]. Some alternative metrics based on social media have also been considered as a tool to measure social engagement [26], but may generally not be indicative of impact of research at society level [27]. Noteworthy, previous analyses have not addressed how the selection of the research strategy may contribute to the research output(s), particularly those that could be conducive to societal impact.

In this follow-up analysis, we explored what methodological approaches (i.e., animal and/or non-animal models and methods, spanning human-based in vitro models, human-derived specimens and patient cohort studies, as well as in silico/computational technologies) were selected in the context of EU projects on AD, BC and PC research funded under the past four framework programmes (FP5, FP6, FP7 and H2020), considering the major research outputs associated with them [15].

The use of animal and non-animal approaches in EU-funded research focused on AD, BC and PC and the diverse outputs associated with these activities

The use of animals in basic and applied biomedical research is often considered unavoidable, despite the possibly associated translational failures, as highlighted in our retrospective analysis [10, 11]. However, when evaluating the design of the research strategy in terms of its potential to contribute to short-to-medium-term societal and public health impact, the use of human-based approaches, encompassing e.g., human cohorts and population studies or the use of human-derived specimens, is generally deemed by researchers as highly relevant to answer research questions. Similarly, epidemiology-based research has significant potential to generate results that are relevant to the original research question and hence translatable [11]. Thus, human-based approaches, especially those involving clinical/observational study design, are possibly more conducive to societal impact. In line with these considerations, a multinational project "Retrosight", when evaluating the translational impact of research on cardiovascular disease and stroke in Australia, Canada and the United Kingdom across 15–20 years, found that including a clinical scope in study design is one of the factors mostly associated with wider (beyond academic) impact [28]. As confirmed in their subsequent publication, clinically-oriented research has greater and wider impact on health policies, practice, and generating health gains, while basic biomedical research has greater academic impact [29]. As a follow-up of this analysis in 2016, RAND Europe carried out three studies to retrospectively assess the impact of funded research in the areas of arthritis, cardiovascular and mental health. By comparing the findings, authors concluded that including diverse expertise in research design (i.e., multidisciplinary), engaging with non-academic stakeholders, focusing on clinical research, avoiding exclusively funding research based solely on academic excellence, correctly planning and assigning grant resources, establishing international collaborations, considering diverse metrics of success, and recognising that broader social and economic impact may originate from few projects, can be considered as the most relevant lessons forming what they called a 'DECISIVE' approach to biomedical and health research funding [30].

When contemplating the potential influence of method choices, particularly the adoption of novel approach methodologies, on the impact of research, in recent years, the development and use of complex in vitro (e.g., organ-on-chip, microphysiological systems, 3D cell models, etc.) and in silico tools (e.g.. machine learning, artificial intelligence) have increased exponentially. For instance, patient-derived cell platforms and tissue-on-chip systems [31–36] have supported drug discovery, and in silico approaches have enabled the creation of virtual cohorts to assess the safety and efficacy of new drugs and medical devices [37, 38]. The translational potential of such innovative technologies if not already tangible, can be foreseen in the near future.

In the present retrospective assessment, we found that when comparing the three selected research areas across the 20 year-funding period, slightly more AD projects made exclusive use of animals (23% across all analysed framework programmes), compared to BC and PC projects (see Table 1 in [15]). Noteworthy, an overall 60% of analysed projects did not consider the use of animals in their research strategy, which account for 56% of the overall budget (see Table 2 in [15]). While this suggests that human-based research has been significantly funded in the EU over the past 20 years, especially in the area of BC and PC research, the use of animals (alone or in combination with other approaches) in AD research has been more predominant. Notably, when considering the temporal dimension, the use of animals has generally increased over time in all the three areas (both in proportion and absolute values), with a more remarkably increasing trend for PC research, compared to AD and BC, for which the use of animals has remained more stable across these subsequent funding programmes.

Projects' outputs linked to basic and applied research-related activities

In the context of this analysis, major project outputs were largely achieved by means of Research and Innovation Actions (RIA) grants, and to a lesser extent European Research Council (ERC) grants, Marie Sklodowska-Curie Actions grants, etc. Professional networking grants such as CSA (Coordination and Support Actions) and diverse mobility grants also played an important role in European capacity building and mutual fertilisation of ideas, dissemination of skills and knowledge [12, 14].

When evaluating the diverse range of research outputs, we initially focused on those closely linked with fundamental and applied research that investigated the role of a molecular pathway or a disease mechanism or the development of a new method/model as outputs. It is known that the EU has been traditionally supporting cutting-edge basic and applied research, and this is confirmed by the relatively high proportion of investment allocated on these types of projects (see Table 3 in [15]). On average, the proportion of projects that focused on basic and applied research and used animal methods was similar to the proportion of projects that did not consider animal approaches. As a confirmation of the aforementioned general trend, the use of animals has been more prevailing in AD than in BC and PC basic/applied research projects. The temporal dimension further showed that, when compared to previous FPs, under H2020, the number of research projects accounting for the use of animals (alone or in combination with other methods) increased. Moreover, animal usage in both AD and PC research has progressively increased over time, remaining quite stable in BC basic and applied research projects.

These trends are confirmed also by the ALURES statistical database reporting animal uses in Europe, which showed that, e.g., in 2018 about 902 thousand animals were used in basic research on the nervous system (including also AD), and about 557 thousand animals were used in basic research on oncology (including also BC and PC) [39]. These numbers further increased in 2019, with about 944 thousand animals used in basic research on the nervous system, and 600 thousand animals used in basic research on oncology.

Outputs with potential for societal impact: new patents, development of drugs and medical devices, clinical trial design and patient stratification

Our recent analyses suggested that projects specifically addressing the designing of novel diagnostic or prognostic tools are generally conducive to short-to-medium term societal impact [10–12]. In addition, patent applications, the development or repurposing of drugs, the creation of a new medical device, and the conduct of a clinical trial, were also considered as tangible outputs indicative of wider (beyond research) impact, serving as indicators of successful translation of biomedical research [15, 40, 41].

When more closely looking at these research outputs, more than half (57%) of the overall FP7 and H2020 projects that contributed to the release of at least one patent did not consider the use of animal approaches, being this percentage a bit lower for AD research projects than BC and PC projects. Noteworthy, in the area of AD, a remarkably higher number of H2020 projects that resulted in patent applications (8 in 11), did not consider the use of animals, whilst this proportion was reversed in FP7.

A significant proportion (nearly half) of the analysed projects addressed drug development, drug treatment or the creation of a medical device, and a bit more than 60% of these made no use of animals. However, the temporal

dimension suggests that the number of AD, BC and PC projects under this output category that used animals has increased in most recent H2020 funding program compared to the previous one (FP7) (i.e., 25 (33%) and 54 projects (45%), for FP7 and H2020 respectively). When comparing the different research areas, whilst the number of AD and BC project proposals that considered the use of animals remained quite stable over time, PC projects based on animal methods remarkably increased under H2020.

In addition, the projects focusing on the development, repurposing or testing of drugs represented a minority (11% of total projects), and most of the overall budget allocated on them (> 80%) covered animal experimentation (see Table 8 in [15]). In general, the percentage of projects making use of animal-based methods was much higher than the percentage of those based on non-animal approaches (64% vs 36% respectively). This is not surprising considering that current legislation for human pharmaceuticals entails testing drugs in animals in non-clinical studies. Compared to FP7, under H2020 a higher proportion of AD, BC and PC projects falling under this output category accounted for animal testing.

On the other hand, most of the funding allocated on projects addressing clinical trials (62%), supported research activities that did not involve the use of animals, being this proportion higher for BC projects, although slightly lower under the most recent funding program (H2020).

In addition, a very small proportion (3%) of analysed projects addressed patients' stratification in their strategy, and the vast majority of them (90%) was based on non-animal research.

Overall these results suggest that, except for projects focusing on drug development, testing or repurposing, for which the use of animals (either alone or in combination with "3Rs testing approaches") is still a mandatory step when searching for market approval [42], most of the projects associated with patents and clinical trial applications (outputs that could be conducive to societal impact [10, 28, 30]), did not entail the use of animals in their research strategy.

Concerning the development of new drugs, the failure rate for chronic/degenerative diseases remains very high, with > 95% of tested drugs failing to receive regulatory approval [43, 44]. Flaws in preclinical experimentation design, the inadequacy of animal models to recapitulate human disease complexity (which is mainly due to interspecies differences in immune system [45], microbiota [46], metabolism [47], and critical developmental, anatomical and physiological features and processes [48–51]), the inappropriate selection of drug targets, overlooking efficacy, pharmacodynamic and pharmacokinetic properties, or inaccuracies with the selection of clinical trial participants, are considered plausible reasons underlying clinical failure in drug development [52]. On a different note, innovative human-relevant approaches and technologies, such as organ-on-a-chip (OoC) microfluidic devices, in recent years have been proven extremely useful to model complex diseases and rare genetic disorders, and better predictors (than animals or simplistic in vitro models) of human responses to pharmaceuticals, toxins, radiation and infectious pathogens [53, 54], paving the way to more efficient drug development and personalised medicine.

Other outputs with translational impact: primary and secondary prevention research activities

To reach the target set in Europe's Beating Cancer Plan, the EC has recently presented a new approach to support Member States to increase their uptake in screening programmes, aiming to offer breast, colorectal and cervical cancer screenings to 90% of those who qualify, by 2025, and to extend screening in order to include prostate, lung and gastric cancers, based on further research [55]. On a similar trend, dementia digital screening tools have been developed over recent years to enhance dementia and mild cognitive impairment early detection [56–58].

In parallel with this, our retrospective analysis showed that about four in ten projects focused on secondary prevention, namely the design and the production of a diagnostic tool. The majority of the projects under this output category did not consider the use of animals in their research design (74%, considering the three research areas altogether), which suggests the important role played by human-relevant approaches/technologies in diagnostic tool development. However, across the four funding cycles, an increasing trend in animal usage was also recorded for all the three research areas, paralleled with a decreasing percentage of projects that made exclusive use of non-animal methods and technologies.

While research and innovation in screening technologies and secondary prevention is important to improve early detection, which clearly has societal impact implications, greater efforts could be made to support primary prevention research and policy interventions. Our analysis showed that 8% of the projects addressed lifestyle and prevention-related research, and the vast majority of them did not account for animals. This prompts the importance to rely on human-relevant research strategies especially when the goal is exploring systemic, multi-dimensional and multi-factorial elements underlying human behaviour and lifestyle, disease aetiology and complexity [59].

When considering nutrition, only three projects covered nutrition or nutrient-related research, and animals

were used in two of them. Moreover, the percentage of projects addressing lifestyle and prevention did not increase and eventually decreased under more recent framework programmes (FP7 and H2020), which does not appear to be a positive metric, considering the important role played by prevention to reduce the risk and manage the burden of chronic and degenerative diseases, such as AD and other forms of dementia, as well as cancer [16–19].

Primary prevention research initiatives could be promoted and better funded, considering that most, if not all, chronic NCDs are largely preventable by means of primary prevention interventions (considering e.g., the role of diet, physical activity, cognitive training, tobacco, alcohol harmful use, sleep quality, environmental pollutants, etc. in the onset of most of these ailments [60]). In line with this, a recent WHO report emphasises the importance to promote physical activity and improve quality of diet in older age to reduce the risk of chronic and degenerative diseases, promote healthy ageing, and increase healthy life expectancy [61]. Notwithstanding, despite chronic diseases on average accounting for up to 80% of EU healthcare costs, preventive healthcare in the EU accounted for (only) 0.37% of GDP in 2020 [62], and prevention medicine and research appear not to be adequately funded across EU Member States, representing only a minor proportion of overall health budgets [63]. Recent evidence-based health promotion and disease prevention can help reduce the prevalence of NCDs by as much as 70% [2]. Therefore, increasing funding on prevention-focused, human-relevant, patient-tailored research may help to tackle public health challenges, reduce health care and public health expenditures, mitigate the burden of AD and dementia and the incidence of cancer.

Other outputs with potential for societal/public health impact

In our analysis we explored some additional outputs associated with innovative technologies, such as imaging technologies, computational approaches, chip technologies (e.g., organ/tissue-on-a-chip), and nanotechnologies, as well as biomarker discovery, which is considered highly relevant to improve early diagnosis [64, 65]. Overall, projects that accounted for these technologies and their relative outputs were financed with a very small proportion of the overall research budget analysed (between 1 and 4%) (see Annex 1, Supplementary Tables S2-S6 in [15]). Notably, for most of these outputs, the design of research proposals was based on non-animal approaches, except for nano-technology-related projects. In addition, when comparing the most recent funding programmes, a higher percentage of H2020 projects that addressed imaging and nano-technologies accounted for animals compared to FP7.

Although projects falling under these output categories represented only a minimal chunk of the overall AD, BC and PC research conducted during this funding period, their impact on public health is foreseeable. In line with this, in more recent years, significant investments have been allocated on these innovative technologies; for instance, OoC research and development have been rapidly growing, supported by dedicated funding and public–private partnerships and initiatives [66]. In EU, a recent RIA action (next generation organ-on-chip, RIA-LS) has supported multidisciplinary research for the development of OoC technologies to mimic human organs based on integrated platforms involving technologies including e.g., multi-tissue or multi-organ culturing, micro-fluidics, micro/nano-sensors, imaging, 3D bio-printing, and bioinformatics, considering also scalability, and standardisation of tools and methods, and taking into account medical regulatory requirements [67]. Noteworthy, OoC predictive capacity has been recently compared to animal models, and in some cases OoCs have been shown to outperform animals in predicting results already obtained in human clinical trials. These complex in vitro technologies can be particularly suitable for analyses that cannot (or are difficult to) be directly carried out in humans, e.g., when testing the effects of high radiation exposures, or the effects of biologics that do not recognise non-human targets, or for modelling a genetic disease that cannot be modelled using different approaches [53].

Regarding imaging technologies, the European Institute for Biomedical Imaging Research (EIBIR) provides support to the development of biomedical imaging technologies with the goal to improve disease diagnosis, treatment and prevention [68, 69]. Along the same line, computational technologies have deepened our understanding of the biological mechanisms underlying disease onset and the factors contributing to inter-patient variability [70], whilst also improving patient care through the development of wearable sensors, genome analysis, disease detection through machine learning, and health informatics models [71]. The EC, during H2020, has supported some projects focused on computational technologies aimed e.g., to develop computer simulations for the testing of new medicines and medical devices [72], and future funding will likely be allocated in upcoming calls for proposals.

In addition, nanotechnologies have evolved in recent years and the rise of nanomedicine has seen the application of these technologies in healthcare, drug delivery, drug discovery (nanotherapeutics), and the development of more sensitive diagnostics [73, 74]. Several projects

on nanotechnology development have been funded by the EU, focused e.g., on nanodiagnostics and nanotherapeutics [75]. The European Technology Platform on Nanomedicine (ETPN) is a European industry-oriented initiative that, since 2005, aims to outline the nanomedicine research roadmap in Europe [76]. Its recent "Strategic Research & Innovation Agenda for Nanomedicine" provides recommendations for prioritisable research on highly prevalent diseases (e.g., cancer, cardio-vascular diseases, diabetes, neurodegenerative diseases, infection diseases, osteoarticular pathologies, etc.), focusing on translatability of research results [77].

The dissemination of scientific knowledge: trends in peer-reviewed publications

Looking at the number and impact factors of scientific publications has traditionally been considered as a practical way to monitor research success, although published studies may not necessarily result in immediate, medium-term, or long-term tangible impacts on public health [78, 79]. Apart from considering the number of publications, our previous analysis also covered the number of citations across the analysed funding period in these three areas of research [12, 14]. However, both citation counts and journal impact factors may be inconsistent indicators of research quality [80], and may arguably be considered as not necessarily indicative of societal impact and research translatability [81]. Notwithstanding, our analysis of peer-reviewed publications highlighted some trends regarding the use of animals or non-animal approaches in these research areas, considering the associated research outputs across funding programmes. In particular, despite animals being still widely used in AD, BC, and PC research, the percentage of articles that were exclusively based on the use of animal approaches has decreased especially in more recent framework programme (see Table 12 in [15]). On the other hand, articles published in the context of projects that accounted for both animal and non-animal approaches, increased in H2020 compared to previous framework programmes. This shift is likely due to a number of factors, including advances in non-animal technologies, ethical concerns, and public pressure. As commented above, while researchers are becoming more interested in using non-animal methods, animal models are still seen as an important part of the research process [10].

Moreover, while the majority of the projects covering patents have based their research strategy largely on non-animal approaches, when looking at publications these percentages changed, with a remarkably high percentage of publications stemming from research proposals with patents that accounted also for animals. This suggests that papers reporting animal studies may more frequently (or more easily) be published than those excluding animal experimentation, as suggested by a recent analysis [82, 83]. Nevertheless, a higher percentage of papers derived from projects with patents and that covered non-animal research was published in more recent funding cycles compared to FP7. This may be indicative of a larger application of innovative non-animal methods and technologies in more recent funding calls, especially those focused on life science, as suggested by a recent analysis of ERC-funded projects that supported research that was subsequently cited in patents [84].

In line with the observations on project numbers, the use of animals is more dominant in articles published in the context of projects that focused on basic research (59%), clinical trials (52%), drug treatment/medical devices (52%) and drug development, testing or repurposing (85%). As explained above, despite their potential limitations, animal models have been largely used in academia to reply to basic or applied research questions, and also in industry, for testing new drugs and treatments during preclinical stages. However, it is worth noting that the percentage of basic research articles that accounted for animals has undergone a decreasing trend (from 80% in FP5 to 61% in H2020).

Regarding the articles from projects that considered the development, repurposing or testing of drugs, we observed a remarkably high percentages of articles from FP6, FP7 and H2020 projects under this output category that considered the use of animals (91%, 85% and 86%, respectively). On a similar note, more than half of the articles associated with clinical trial made use of animal methods especially in projects focused on AD research.

Conversely, most of articles from projects that mentioned lifestyle, prevention, diagnostic tools, and patient stratification did not involve animals. This suggests that non-animal methods are being used to study the role of lifestyle and prevention in cancers and AD research. One remarkable exception is represented by those articles (especially on AD) that focused on nutrition-related research, which all involved the use of animals, despite the notable interspecies differences in e.g., gut microbiota composition [46, 85], glucose metabolism and insulin sensitivity [86].

Noteworthy, when comparing the three research areas, a decreasing trend in the percentage of BC papers accounting for animal experimentation was recorded under H2020 compared to FP7. This decline was particularly evident in outputs linked to patent filings, diagnostic tools, drugs, treatments, and medical devices, while publications associated with AD and PC showed a different trend. In the context of H2020, all research publications pertaining to AD and PC focused on drug development, testing and repurposing involved

animal studies. Although both animal and non-animal methods have their limitations, the extensive reliance on animal studies in preclinical research, as indicated by these findings, could be seen as a potential contributor to the high rate of drug attrition within these research areas [43, 44, 87].

Finally, as for projects addressing innovative imaging and computational technologies and biomarker discovery, most of the scientific publications generated in the context of these research activities, although representing a minimal proportion of the overall number of articles published during this funding period, were largely based on non-animal methodological approaches (between 75 and 100% of the papers covering these research outputs). On the other hand, the relatively few papers published in the context of nano-technologies, mostly accounted for animal models (82%). Notably, the majority of the AD studies (73%, under FP7) published in the field of chip technologies, accounted for animal methods. This again suggests that, at least in some fields, studies involving animal experimentation may have a greater likelihood of being published compared to studies that do not involve such experimentation [82, 83].

Conclusions

Overall, our findings suggest that the use of animals has been more prevalent in AD research compared to BC and PC EU-funded basic research, and that in more recent funding cycles (H2020), the number of research projects involving animal use has increased. Similarly, projects focusing on drug development, testing, or repurposing heavily relied on animal experimentation, which still constitutes a legal requirement for obtaining market approval of new pharmaceutical compounds. Conversely, most projects associated with clinical trial design, patient stratification, diagnosis and/or diagnostic tool development, lifestyle and/or prevention, have predominantly based their research strategies on non-animal methods and technologies. Similarly, cutting-edge research encompassing the development and utilisation of imaging, computational, organ/tissue chip technologies and biomarkers has primarily relied on non-animal research strategies, although an increasing use of animals was noted over time for nanotechnology-related projects.

While the absolute number of AD, BC, and PC projects focused on these cutting-edge applications has been relatively low in the past two decades, the contribution of these technologies to innovation in diagnosis, prevention, treatment of diseases, and healthcare is expected to significantly increase with time, along with the proliferation of calls for proposals focusing on these technologies in future funding programs.

Notably, a higher percentage of studies was published in the context of projects addressing topics such as nutrition, chip- or nano-technologies that considered animal experimentation than those not accounting for animal use.

Particularly concerning is our retrospective analysis indicating a decrease in the percentage of projects addressing lifestyle and prevention under more recent funding cycles, despite AD, BC, PC, as well as most of NCDs have been proven to be largely preventable [16–19]. This highlights a trend that warrants consideration in the design of future framework programs.

A second major use of public health indicators is accountability. Such indicators serve as a semi-quantitative evidence base for governments, health professionals, funding bodies, and the general public to gather information on risks, patterns, and trends related to health, and whether expectations for performance are met. The three disease areas covered in our study represent primary global concerns and unmet medical needs, necessitating local, national, and international measures and policies. Sustained progress in the prevention, diagnosis, and treatment of these diseases requires investment in a robust ecosystem of research and innovation that prioritises human-relevant research strategies to achieve public health impact and improve the translatability of funded research.

As a final note, fostering effective dialogue among the research community, citizens, and policymakers is essential to catalyse societal impact [24].

Supplementary Information

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Supplementary material 1.

Author contributions

Conceptualisation: PD, AG, MM, FP; Writing—Original Draft Preparation: PD, AG, MM, FP; Writing—Review and Editing: PD, AG, MM, FP; Final Review and Editing: PD, AG, MM, FP; Project Administration: PD. All authors have read and agreed to the published version of the manuscript.

Data availability

The entire data set of this retrospective analysis is stored in the JRC Data Catalogue: https://data.jrc.ec.europa.eu/dataset/a96ad0dd-f23a-4ee4-a839-04928c1c5cf3. Original data described in this manuscript are reported in the JRC Technical report: https://publications.jrc.ec.europa.eu/repository/handle/JRC138356.

Declarations

Competing interests

The authors have no competing interests to declare.

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