

POLICY BRIEF

Repurposing of medicines in oncology – the underrated champion of sustainable innovation



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Abbreviations

COVID-19	coronavirus disease of 2019
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CUSP9v3	coordinated undermining of survival paths [regimen]
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DARWIN EU	Data Analysis and Real World Interrogation Network of the European Union
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ESMO	European Society for Medical Oncology
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EU	European Union
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FDA	United States Food and Drug Administration
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GBM	glioblastoma multiforme
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RCT	randomized controlled trial
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ReDO	Repurposing Drugs in Oncology [database]
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Key messages

- ◆ Repurposing is a strategy to identify new uses for approved or investigational medicines outside the scope of their original medical indication.
- ◆ While delivering innovation (new treatments that resolve unaddressed health needs), repurposing also offers several advantages over de novo (from scratch) development, such as lower costs of development, lower risk of failure and reduced time frame to registration.
- ◆ Across almost all cancer types, many products are already commonly used off-label – in particular, for patients who have no alternative options. Off-label use means that patients receive a medicine without a clearly established benefit–risk ratio.
- ◆ Non-commercial repurposing of off-patent medicines for cancer treatment has the potential of addressing currently unmet needs in a cost-effective way, especially in areas that are not attractive for the industry, such as rare cancers. Collectively, rare cancers account for around 22% of new cases in Europe.
- ◆ While repurposing previously relied on an ad hoc discovery process, it has more recently evolved to rely on implementation of organized, systematic, data-driven approaches to identify suitable candidates. In most cases, these approaches integrate computational assistance. Big Data and artificial intelligence are increasingly used for this purpose.
- ◆ Traditional models of collecting clinical evidence may not always offer the optimal route for repurposing owing to the high costs involved and the applicability of established pharmaceutical development and testing paradigms for some repurposing approaches, such as those focusing on combination therapies.
- ◆ Only the marketing authorization holder of a given medicine can currently apply for an extension or variation of its marketing authorization. Even if non-commercial clinical trials confirm the efficacy of a repurposed drug, patient access to these treatments depends on the willingness of a pharmaceutical company to obtain authorization for the new indication and to take responsibility for its risk management.
- ◆ Returns on investment for repurposed off-patent medicines are expected to be low or nil, and pharmaceutical developers are rarely interested in pursuing repurposing opportunities, even when clinical evidence is made readily available by other stakeholders. Existing European Union (EU) schemes (such as those on data exclusivity and orphan designation) aimed at promoting off-patent drug repurposing do not offer the usual level of incentives for the industry compared to alternative investments, and they are underused.
- ◆ Several potential solutions (Table 1) have been identified to facilitate non-commercial

repurposing. They include reducing the risk of failure by improving the selection of candidates, facilitating generation of clinical evidence, streamlining regulated processes, amending restrictive legislation, improving collaboration and coordination between stakeholders and ensuring adequate funding.

- ◆ Non-commercial drug repurposing is supported by the Europe's Beating Cancer Plan and the EU's 2020 Pharmaceutical Strategy for Europe. A European Commission pilot project with the engagement of non-commercial champions (not-for-profit or academic stakeholders) and industry is planned in 2021. Its implementation will provide valuable information for future EU steps to facilitate repurposing of off-patent medicines for cancer.

- ◆ A successful EU repurposing strategy will require coordination among several sectors in the current pharmaceutical system. A “one-stop shop” mechanism could be established for non-commercial champions at the EU level: this would coordinate relevant EU institutions in funding research and assisting with development of the scientific arguments required to obtain regulatory approval for repurposed financially unattractive medicines.
- ◆ Public–private partnerships involving research, registration and manufacturing (guaranteed volumes for non-profitable compounds) of repurposed medicines for cancer could also be explored to combine the skills and resources of both the public and private sectors through sharing of risks and responsibilities.

Table 1. Short overview of issues and solutions in repurposing of off-patent medicines for cancer

Topic	Issue	Potential solution
Improving selection of candidates	Risk of clinical failure or adverse event	Artificial intelligence and use of Big Data
Generating clinical evidence required by regulators	Lack of regulatory experience among non-commercial champions	Early scientific advice and regulatory assistance throughout the process
	Applicability, time and cost	Exploring the potential for greater reliance on real-world data, data networks, adaptive platform trials and innovative trial designs
Streamlining regulatory pathways	Administrative fees	Reducing fees for repurposing of financially unattractive medicines
	Only industry allowed to apply to obtain authorization for new indications	Removing barriers for non-commercial champions
Improving stakeholder collaboration and coordination	Coordination between EU institutions and organizations	An EU one-stop shop for non-commercial repurposing
		A European network of experts
	Poor cooperation between industry and non-commercial champions	Encouraging working together to obtain regulatory approval and sharing of data on shelved products not protected by patents
Ensuring funding	No prioritization mechanisms	A European list of priority indications
	Poor availability of funding	More funding from public sources
		Exploring the viability of novel funding mechanisms
		Public–private partnerships to combine skills and resources of both public and private sectors

Introduction to drug repurposing

Drug repurposing (also called drug repositioning, reprofiling or retasking) is a strategy to identify new uses for approved or investigational medicines that are outside the scope of the original medical indication (1). New treatments are sought mainly from products that are already in use, but also from compounds that have been shelved, withdrawn or abandoned because they did not perform as expected in their primary designated indications or because better therapies emerged. This report discusses non-commercial establishment of new cancer treatments by using off-patent products relying on both “hard repurposing” (repurposing of non-cancer medicines for oncology use) and “soft repurposing” (adding new cancer indications for established cancer medicines) approaches (2). The concept of repurposing has gained in popularity over the last decade. The number of publications related to drug repurposing or repositioning has grown exponentially (3), and a review published in 2018 identified 190 ongoing late-stage oncology trials researching products that had been licensed for non-cancer indications (4). The Repurposing Drugs in Oncology (ReDO) database, curated by Belgian non-for-profit organization the Anticancer Fund, lists a total of 335 non-cancer drugs that have shown some evidence of anticancer activity. Of these, 84% are off-patent and over 90% have some in vivo evidence from peer-reviewed studies: medical case reports, observational studies or clinical trials. All this provides hope for a promising pipeline of treatments for cancer that could address some of the current unmet therapeutic needs.

In addition, answering unmet medical needs through drug repurposing has recently received further attention from the medical community because of the global coronavirus disease of 2019 (COVID-19) pandemic. The lack of effective therapies for the SARS-CoV-2 pathogen highlighted the need to find treatments that can be applied quickly to reduce mortality and morbidity. Repurposing was identified as one main strategy to provide a fast and cost-efficient approach to this purpose (5). It resulted, for instance, in the establishment of corticosteroids as the backbone of therapy for patients with severe and critical COVID-19 (6).

Nevertheless, the potential to provide new cancer treatment options through drug repurposing has so far been left largely untapped. In 2017, as few as four repurposed drugs were included in the guidelines of the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network of the United States of America (7).

Advantages of repurposing versus de novo development

The disease burden of cancer in the European Union (EU) has increased over time, to a large extent as a result of population ageing. In 2020, it was estimated to have risen to 2.7 million new cases (all types, excluding non-melanoma skin cancer) and 1.3 million deaths (8). Costs of cancer care have also risen, due in part to rising numbers of patients diagnosed with the disease and in part to new treatments involving costly anticancer medicines. In 2018, the total cost of cancer in Europe¹ was estimated to have reached €199 billion, of which cancer drugs accounted for €32 billion. Total estimated costs of cancer care per inhabitant differed widely between countries: the highest rate was 3.6 times the lowest (after adjustment for price differentials), in part due to large disparities in access to contemporary effective therapies (9). These disparities were also highlighted by an ESMO study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe, which reported substantial differences in formulary availability, private expenditure and actual availability of many anticancer medicines (10).

Echoing the worries of European cancer experts, the Council of Europe expressed concern about the “exorbitant” price of cancer medicines (11), and the Council of the European Union (12) noted:

an increasing number of examples of market failure in a number of Member States, where patients’ access to effective and affordable essential

medicines is endangered by very high and unsustainable price levels, market withdrawal of products that are out-of-patent, or when new products are not introduced to national markets for business economic strategies.

The Commission’s ambitious Europe’s Beating Cancer Plan also places strong focus on addressing cancer-related inequalities between and within countries, with actions to support, coordinate and complement Member States’ efforts (13).

Despite the high levels of expenditure and improved availability of new medicines, however, many types of cancer lack adequate treatment options and are still associated with unfavourable outcomes across countries. This is particularly the case for rare cancers, which collectively account for around 22% of new cases in Europe (14). Important unmet needs also remain in metastatic cancers and those that have not responded to previous treatment (15). Moreover, if outcomes of treatment are to be improved, it is increasingly recognized that multiple anticancer therapies will need to be used in combination to achieve greater efficacy and to prevent cancers becoming resistant to treatment (16), further increasing the cost of care.

Finally, a large number of products are already commonly used off-label across almost all cancer types. This is particularly the case for patients who have no alternative options – for example,

¹ This includes the 27 EU countries plus Iceland, Norway, Switzerland and the United Kingdom.

in indications where no drugs are approved or for patients who have exhausted standard lines of treatment (17). While off-label drug use may sometimes be clinically justified, however, it is associated with a number of safety, legal and ethical issues. It can jeopardize patient safety in certain clinical scenarios where a positive benefit–risk ratio is not fully established (18). Thus, establishing rigorous scientific evidence and repurposing the vast arsenal of existing approved medicines, with established safety profiles, may be an attractive strategy to offer more effective treatment options to patients with cancer (16).

While delivering innovation (new treatments that resolve unaddressed health needs), repurposing of existing medicines can also offer a wide range of advantages over de novo development. Licensed medicines have readily available data on pharmacokinetics, pharmacodynamics and posology. Knowledge of safety and toxicity – including rare adverse events and understanding of mechanisms of action and/or molecular targets – has been developed, and clinical experience has been derived from use in the original indications (19). If dose compatibility is found – meaning that the required strength for the new indication is equal to or lower than that used for the original indication (20) – much of the available preclinical testing, safety assessment and even Phase 1 clinical trials can reliably be used for the new indication and do not have to be repeated. As a result, the time frame for drug development can be reduced because most of the preclinical testing, safety assessments and, in some cases, formulation development have been completed.

At the same time, the risk of failure is lower: if the repurposed drug has already been found to be sufficiently safe in preclinical models and for humans in early-stage trials, it is less likely to fail – at least from a safety point of view – in subsequent efficacy trials. Moreover, less investment is needed, although this will vary greatly depending on the stage and process of development of the repurposing candidate (21). The costs of bringing a repurposed drug to market have been estimated at US\$ 300 million on average, compared with an estimated US\$ 2–3 billion for a new chemical entity (22). It is important to note that many of the products that are potentially suitable for repurposing have already lost patent protection and are thus substantially more affordable than new cancer drugs. This could have a positive impact on the cost and cost–effectiveness of cancer therapies internationally and, as a result, on access in general and disparities in access between countries.

How repurposing is done

Most of the best known examples of medicines that have been successfully repurposed in the past – such as sildenafil, minoxidil, aspirin and valproic acid – have emerged from ad hoc discovery processes, often relying on chance observations or the known pharmacology of a drug (such as an off-target adverse effect²) to solve clinical problems from other domains (23). Clinicians have played a major role in the discovery of such off-label therapies (24). Retrospective observational studies of patients with cancer who are taking potential candidates for repurposing are, however, often limited by immortal time bias³ and selection bias (25), which may overestimate effects.

In recent years, identification of candidates has evolved to rely on the implementation of organized, systematic, data-driven drug repurposing approaches, which in most cases integrate computational assistance (26) (Table 2). Big Data and artificial intelligence are increasingly used in the process. For instance, *in silico* approaches (those solely relying on computational methods) usually combine knowledge mining with molecular modelling methods to identify new potential drug–target interactions. These methods rely on algorithms to screen a wide range of molecules to see whether and how they interact with target proteins.

Identifying the right candidate medicines for an indication of interest with a high level of confidence is critical, and this is where modern approaches

for hypothesis generation are most useful. These systematic approaches can be subdivided into computational (molecular docking, genetic association, retrospective clinical analysis, etc.) and experimental approaches (phenotypic screening and binding assays to identify relevant target interactions) both of which are increasingly used synergistically (26).

Once a shortlist is created, validation steps can be performed *in vitro* and *in vivo*. Research can progress to assessment of the drug effect in preclinical models and evaluation of efficacy in clinical trials, assuming that sufficient safety data are available from Phase 1 studies undertaken as part of the original indication. Traditional models of collecting evidence on efficacy may, however, not always offer the optimal route for repurposing. For instance, the established pharmaceutical development and testing paradigm is not designed to support the testing of combination therapies, with very few exceptions (27). This is particularly problematic for therapies combining repurposed drugs with conventional chemotherapeutics as part of synergistic combinations. Furthermore, a number of candidates for repurposing lack single-agent activity in cancer, and cannot be assessed in uncontrolled, Phase 2 studies, which have become common in oncological research. These drugs require assessment in randomized controlled trials (RCTs). Many such trials must have a large sample size to account for the size of the effect, resulting in substantial costs (25).

2 Off-target adverse effects are those that can occur when a drug binds to targets (proteins or other molecules in the body) other than those to which it was meant to bind. This can lead to unexpected side-effects that may be harmful.

3 Immortal time bias refers to time in the observation or follow-up period during which the primary outcome of the study (such as death) cannot occur in one treatment group. For example, patients with cancer who take so-called repurposed medications must live long enough to receive these drugs, but this does not apply to the control group.

Selected successful and candidate medicines repurposed for cancer treatment

Several off-patent medicines have already been successfully repurposed for cancer treatment or are currently undergoing clinical research. Table 2 provides an overview of some of the most notable examples that have already enriched or that could enrich the arsenal of medicines used in oncology.

Table 2. Selected successful and candidate medicines repurposed for cancer treatment

Medicine and original indication	Repurposed cancer indication	Main findings
Thalidomide – sedative, targeted at pregnant women to treat morning sickness	Multiple myeloma	<p>Thalidomide was originally marketed in the late 1950s and withdrawn because of links with severe skeletal birth defects in children born to mothers who had taken the drug in the first trimester of their pregnancies. Its potential benefit in cancer treatment was first hypothesized in the 1960s, shortly after the teratogenic properties were reported, and the discovery of potent anti-angiogenic properties in the 1990s renewed interest in its use as an antitumor agent.</p> <p>Following extensive clinical research, thalidomide was first approved in 2006 by the United States Food and Drug Administration (FDA) for use in combination with dexamethasone in patients with newly diagnosed multiple myeloma (28).</p> <p>It was also authorized in the EU in 2008, in combination with melphalan and prednisone, and is indicated as first-line treatment of patients with untreated multiple myeloma who are aged 65 years and over or ineligible for high-dose chemotherapy (29).</p>

Table 2 contd

Medicine and original indication	Repurposed cancer indication	Main findings
Acetylsalicylic acid – analgesia	Colorectal cancer prevention	<p>Acetylsalicylic acid (aspirin) has been in use for analgesia since the late nineteenth century. Observational evidence indicating a reduction in the risk of colorectal cancer after prolonged use started to emerge in the late 1980s (30).</p> <p>In 2016, following a number of studies, the U.S. Preventive Services Task Force released a Final Recommendation Statement on initiating low-dose aspirin use for the primary prevention of cardiovascular disease and colorectal cancer in adults aged 50–59 years who have a 10% or greater 10-year cardiovascular disease risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years and are willing to take low-dose aspirin daily for at least 10 years (31).</p>
Cimetidine – duodenal and benign gastric ulceration	Resected colorectal cancer	<p>Anecdotal reports of tumour regression with histamine type 2-receptor antagonists have led to a series of trials with this class of drug as adjuvant therapy to try to improve outcomes in patients with resected colorectal cancers.</p> <p>In 2012, the Cochrane Collaboration published a systematic review concluding that cimetidine appears to confer a survival benefit when given as an adjunct to curative surgical resection of colorectal cancers. The review also noted that further prospective randomized studies are warranted (32).</p>
Raloxifene – osteoporosis	Breast cancer prevention	<p>The potential of repurposing raloxifene for breast cancer was first announced by the Multiple Outcomes of Raloxifene Evaluation randomized trial – a multicentric study conducted in 180 hospitals in 25 countries – in 1999. Although breast cancer risk reduction was not a primary end-point for the trial, it demonstrated that, among postmenopausal women with osteoporosis, the risk of invasive breast cancer decreased by 76% during three years of treatment (33).</p> <p>Other trials followed and confirmed the results. The FDA approved raloxifene for the prevention of invasive breast cancer in 2007 (34).</p>

Table 2 contd

Medicine and original indication	Repurposed cancer indication	Main findings
Nine-drug cocktail	Investigated in glioblastoma multiforme (GBM)	<p>A number of multidrug regimens that involve using repurposed agents with standard treatments are being investigated for the treatment of GBM. These regimens target multiple pathways in the hope of inducing a greater overall effect than monotherapy. One cocktail is the coordinated undermining of survival paths regimen (CUSP9v3), which uses nine drugs (35).</p> <p>In February 2021, the researchers revealed that CUSP9v3 can be safely administered in patients with recurrent GBM under careful monitoring. A randomized Phase 2 trial is in preparation to assess the efficacy of the CUSP9v3 regimen in GBM (36).</p>
Zoledronic acid – osteoporosis	Used and investigated in breast cancer	<p>ESMO considers adjuvant bisphosphonates to be standard therapy for postmenopausal women with hormone receptor-positive breast cancer, contributing to reduced recurrence and breast cancer mortality (37).</p> <p>The results of the Phase 3 Hormonal Bone Effects trial published in 2019 provide evidence of their benefit in premenopausal patients as well (38).</p>
Propranolol – high blood pressure, irregular heartbeat and similar	Investigated in angiosarcoma	<p>A pilot neoadjuvant window-of-opportunity study is being performed to explore the activity of propranolol monotherapy in angiosarcoma. The study consists of a single arm: propranolol is administered as monotherapy. When patients are diagnosed, standard anticancer treatment is scheduled in six weeks, while propranolol treatment can start immediately after diagnosis and is continued until the day the standard anticancer treatment is started (39).</p>
Acetylsalicylic acid – analgesia	Investigated in several early-stage cancers	<p>Add-Aspirin is a large RCT, currently taking place in the United Kingdom, Ireland and India. It will recruit 11 000 participants to help find out whether regular aspirin use after treatment for early-stage cancer (breast, colorectal, gastro and prostate) can stop the cancer coming back and help prevent deaths (40).</p>

Selected ongoing initiatives

The repurposing community has been very active in recent years. Ongoing initiatives include academic open-access repositories with information on clinical cancer expression datasets, not-for-profit organizations focused on clinical research and policy, and government and EU programmes that aim to provide comprehensive long-term impacts. The following list provides basic information and links to some of the more notable initiatives.

The **Anticancer Fund (41)** is a Belgian private not-for-profit foundation established in 2013, which aims to generate evidence-based information about cancers and therapies. Its objective is to expand the number of possible treatment options for cancer. In terms of research, the Anticancer Fund works with universities, hospitals and other stakeholders to set up investigator-driven clinical trials. It also operates the ReDO database, which lists non-cancer drugs that have shown some evidence of anticancer activity. Data come from peer-reviewed studies: medical case reports, observational studies and clinical trials.

The EU's **Data Analysis and Real World Interrogation Network (DARWIN EU) (42)** is a coordination centre being set up by the European Medicines Agency to provide timely and reliable evidence on the use, safety and effectiveness of medicines for human use. DARWIN EU will enable the European Medicines Agency and national competent authorities in the European Medicines Regulatory Network to use real-world evidence from across Europe to support regulatory decision-making by:

- ♦ establishing and developing a catalogue of observational data sources for use in medicines regulation;
- ♦ providing a source of high-quality, validated real-world data on the uses, safety and efficacy of medicines; and
- ♦ addressing specific questions through high-quality, non-interventional studies, which include developing scientific protocols, interrogating relevant data sources and interpreting and reporting study results.

DARWIN EU will also contribute to developing the European Health Data Space and the joint action to deliver European principles for the secondary use of health data, known as Towards European Health Data Space. Acting as an early flagship “pathfinder”, DARWIN EU will enable the exchange of health care data for use in health care delivery, policy-making and research across Europe, while fully complying with data protection requirements.

DRUGSURV (43) is a resource for repositioning of approved and experimental drugs in oncology, based on patient survival information derived from clinical cancer expression datasets. It is a comprehensive informatics resource to explore the potential of around 1700 FDA-approved drugs and around 5000 experimental drugs to target (affect) genes that are significantly associated with survival in clinical cancer expression datasets. The resource currently covers 17 different cancer types and around 50 independent clinical expression datasets annotated with patient survival information.

The Repurposing Medicines in the National Health Service in England programme (44) has recently been established in the United Kingdom to identify and pursue opportunities to strengthen the evidence base, licensing, supply, cost–effectiveness and equitable adoption of currently un-licensed or off-label medicines, where there is benefit to the health service and patients. The programme has great potential to affect clinical practice, as all relevant national institutions – including regulators, clinical research funders, health technology assessment agencies and payers – participate in its development and operation.

The United Kingdom's **Innovative Licensing and Access Pathway** (45) aims to accelerate time to market, facilitating patient access to medicines. These medicines include new chemical entities, biological medicines, new indications and repurposed medicines. The Pathway is open to

both commercial and non-commercial developers of medicines (based in the United Kingdom and globally). It comprises an innovation passport designation and a target development profile, and provides applicants with access to a toolkit to support all stages of the design, development and approvals process, enhancing regulatory and other stakeholder input.

The **Drug Repurposing Hub** (46) is a curated and annotated open-access repository of close to 7000 compounds, many of which have been approved by the FDA. Researchers at the Hub have curated and verified these compounds, and are now testing them against disease cell lines. They are also using this resource to glean new insights into the characteristics of disease – efforts that may also jumpstart new drug discovery programmes. The Hub was developed by the Broad Institute in the United States.

Financial and regulatory barriers

While the wide availability and affordability of generic medicines that could potentially be repurposed for cancer treatment provides hope for improving access to cost-effective care and improving health outcomes, it also acts as a strong disincentive for commercial investment in repurposing. Existing EU schemes aimed at promoting drug repurposing include one year of data exclusivity granted for a new indication for a well-established medicine (47). Various provisions under the orphan designation scheme should also facilitate providing a return on investment. These have been criticized for not offering sufficient incentive for the industry and for being underused, however (48–49). As the return on investment for repurposed off-patent medicines is expected to be low or nil (50–51) – or in any case lower than for alternative investments in new products – pharmaceutical developers and their shareholders are rarely interested in pursuing repurposing opportunities. Since these medicines are financially unattractive, they have been referred to in the literature as “financial orphans” (52). To illustrate this, of the 190 clinical trials identified by the ReDO database in 2018, fewer than 4% were commercially sponsored. Repurposing of off-patent medicines is mainly studied non-commercially by researchers from academia, research institutes or collaborative groups (4, 53), and relies on scarce public or philanthropic funding.

In addition, the current regulatory framework scarcely considers non-profit, academic or public involvement in the research and development of

repurposed drugs. For example, at the EU level, only the marketing authorization holder can apply for a marketing authorization extension or variation of a specific drug. Even if non-commercial clinical trials confirm the efficacy of a repurposed drug, patient access to these treatments will depend on the willingness of a pharmaceutical company to obtain authorization for the new indication. For financial reasons and because of lack of experience or motivation among producers of generics, this is often absent. In addition, non-commercial champions are often unaware of precisely what evidence needs to be submitted as part of an application for marketing approval or label extension for a new indication – for example, whether large RCTs are always required or the choice of clinical end-points (54).

Potential solutions

Several potential solutions have been identified to facilitate non-commercial drug repurposing, some of which are discussed in the literature (15, 55–57). They include a wide array of options such as increasing public funding or exploring novel funding systems for research, relying on innovative technologies in the identification of candidates and changing the way clinical evidence is developed so that it is faster and less costly. From a regulatory perspective, solutions range from streamlining existing processes to designing a novel regulatory framework that would empower non-commercial

stakeholders in regulatory matters. The overview in Table 3 structures the solutions by the issues they attempt to resolve: reducing risk by improving selection of candidates, facilitating generating clinical evidence, streamlining regulated processes, amending legislation to empower non-commercial champions, ensuring adequate funding and improving collaboration and coordination of stakeholders. Each issue is explored further in the following sections. The potential solutions are complementary.

Table 3. Potential solutions for facilitating repurposing of cancer medicines

Issue	Solutions
Reducing risk of failure by improving selection of candidates	Investing further in artificial intelligence and use of Big Data in Europe
Facilitating generation of clinical evidence	Regulators providing assistance and early scientific advice regarding data collection and analysis required for regulatory approval free of charge
	Exploring the potential for greater reliance on real-world data for the generation of clinical evidence
	Exploring the potential for greater reliance on adaptive platform trials/innovative trial designs for the generation of clinical evidence

Table 3 contd

Issue	Solutions
Streamlining regulated processes	Removing administrative fees that pose an additional barrier for repurposing of financially unattractive medicines and/or considering providing encouragement to this purpose
Amending legislation to empower non-commercial champions	Removing restrictions on the entities eligible to apply for market authorization (label) extensions, while entitling the regulator to order labelling changes
Improving collaboration and coordination between stakeholders	Developing a “one-stop shop” for non-commercial repurposing at the EU level
	Encouraging cooperation between non-commercial champions providing evidence and pharmaceutical companies obtaining authorization for new indications
	Encouraging companies to share available data on shelved products that are no longer protected by patents
	Establishing a European “network of experts” to prevent duplication of effort and to promote cooperation
Ensuring adequate funding	Establishing a European list of priority indications with high unmet need to target research funding
	Providing more public funding for non-commercial repurposing from various public sources
	Exploring the viability and potential of funding repurposing through novel mechanisms such as social impact bonds and crowdfunding
	Engaging in public–private partnerships to improve research in repurposing and registration of non-profitable compounds, including manufacturing, where necessary

REDUCING RISK OF FAILURE BY IMPROVING SELECTION OF CANDIDATES

Further European investment may be warranted in the development of artificial intelligence and use of Big Data to screen candidates suitable for repurposing. Recent experience from the COVID-19 pandemic attests to the potential of these approaches (58–59).

FACILITATING GENERATION OF CLINICAL EVIDENCE

Waiving fees for guidance on regulatory aspects of non-commercial repurposing projects would help champions ensure that the evidence they generate is in line with regulatory requirements. For the most part, such champions lack the required experience, and consultancy options are not commonly used and have high rates.

Although most commonly discussed in the context of patented medicines, expanding the use of real-world data – defined as “data related to health care status, routinely collected from a variety of sources, outside of randomized clinical trials” (60) – may hold particular potential to have a substantial impact on drug development and pharmaceutical regulation for repurposed medicines. When robust evidence is available for the original indication, the generation of evidence on the effectiveness of repurposed medicines could be supported by a graded release of a medicine into the general population, combined with real-time analysis of patient responses (both therapeutic and adverse) (61). The approach is still nascent and subject to a number of hurdles, ranging from data standardization, availability and quality to lack of regulated research standards and methodologies. Nevertheless, use of real-world data to inform regulatory decisions on drug effectiveness

is increasing, and the benefit–risk balance (62) and its application in repurposing may positively affect scientific development and regulatory assessment.

Adaptive platform trials or innovative trial designs could also be pursued to the same purpose.

STREAMLINING REGULATED PROCESSES

Removal of administrative fees that pose an additional barrier for repurposing of financially unattractive medicines and/or considering provision of encouragement to this purpose could also be considered to increase motivation for industry to engage in label extensions.

AMENDING LEGISLATION TO EMPOWER NON-COMMERCIAL CHAMPIONS

A more radical solution – one that would require changes to current legislation – proposes removing restrictions on the entities eligible to apply for marketing authorization extensions, with the regulator being entitled to order labelling changes. This would enable non-commercial champions to pursue obtaining authorization for new indications independent of the industry.

IMPROVING COLLABORATION AND COORDINATION BETWEEN STAKEHOLDERS

A successful EU repurposing strategy requires coordinated action among several sectors in the current pharmaceutical system. Developing a one-stop shop mechanism for non-commercial champions at the EU level would facilitate coordination of relevant institutions funding research and assisting champions in developing the scientific arguments required to obtain regulatory

approval for repurposed financially unattractive medicines. National and European organizations that develop clinical guidelines should also be included to ensure that repurposed medicines are considered for inclusion in clinical practice guidance.

Further efforts could be invested at the EU level to encourage cooperation between non-commercial champions and pharmaceutical companies in obtaining authorization for new indications, once the evidence base is developed as required by regulators.

Promoting sharing of relevant data by the industry to support research by non-for-profit organizations – in particular for shelved products that are no longer patent protected – would help avoid the costs and effort required to obtain non-clinical and early clinical data that are already available.

Greater European collaboration could help to avoid duplication of effort and fragmentation – for example, by establishing a European network of experts, as proposed for the assessment of off-label indications.

ENSURING ADEQUATE FUNDING

Increased funding for non-commercial repurposing from the EU and national levels should be coupled with establishment of a European list of priority indications with high unmet need to target research funding.

Novel funding systems could also be explored, even though they do not currently appear to have the potential to offer a comprehensive financial solution for non-commercial repurposing that would eliminate the need for public funding, especially for costly RCTs. Crowdfunding (raising small donations

from a large number of people) has been identified as an option for lowering the risk of early-stage projects and increasing their chance of success in obtaining traditional research grants. High overhead and administrative costs have been raised as concerns, however, as well as the fact that research into rare diseases may be at a disadvantage since it might not generate adequate public concern as it does not address the highest unmet medical needs from a population perspective. Social impact bonds – also referred to as pay-for-success financing – could be developed as formal agreements between outcome payers (governments) and not-for-profit research organizations, in which the latter would be paid their upfront fees (plus a return) should the desired outcome (repurposing) be reached. This model could be used for financing of RCTs. The concept assumes that such an arrangement would result in improved outcomes, reduced care needs and savings for health systems, and that a proportion of these would be shared. Issues that have been identified as barriers include:

- ◆ the ease of defining easily quantifiable and robust outcomes to demonstrate the social impact and cost savings;
- ◆ the long duration and low success rates of most clinical trials;
- ◆ the capacity to secure commitment from governments; and
- ◆ the ability of non-commercial organizations to raise the upfront funding.

Public–private partnerships involving research, registration and manufacturing (guaranteed volumes for non-profitable compounds) of repurposed medicines for cancer could also be explored to combine the skills and resources of both the public and private sectors through sharing of risks and responsibilities.

Alignment with EU strategic documents and the EU repurposing pilot project

Repurposing of off-patent medicines and some of the solutions presented are fully aligned with major EU strategic documents. The Europe's Beating Cancer Plan recognizes that repurposing of existing medicinal products can be a viable strategy to reduce time frames, decrease development costs and improve success rates (13). The 2020 Pharmaceutical Strategy for Europe (63) includes "Delivering for patients: fulfilling unmet medical needs and ensuring accessibility and affordability of medicines" as one of its core objectives. Further, under the objective "Supporting a competitive and innovative European pharmaceutical industry", the Strategy elaborates that:

the Commission supports initiatives to improve academic researchers and not-for-profit stakeholders' regulatory knowledge via scientific and regulatory advice so that the evidence they generate can be seamlessly used to repurpose off-patent medicines for new therapeutic uses. Industry engagement and partnership in this process will be promoted.

Other actions planned by the Strategy relevant for drug repurposing include supporting the use of Big Data and artificial intelligence in drug discovery and a greater emphasis on considering real-world evidence in the process. The Strategy states that "high performance computing and artificial intelligence can help accelerate the identification

of potential active substances for repurposing and reducing the high failure rates". Further, the Commission proposes revising the pharmaceutical legislation to consider how new methods of evidence generation and assessment – such as analysis of Big Data and real-world data – could support the development, authorization and use of medicines.

A European Commission pilot project with the engagement of industry and academia to inform possible regulatory action is planned in 2021 as a Flagship Initiative on Innovation. It was developed based on the Pharmaceutical Committee's 2019 proposal for a framework for the repurposing of established medicines (64). Notably, it proposes that the regulator, the European Medicines Agency or national competent authorities should assist the champion (generally seen as a non-for-profit organization) in assessing eligibility and provide guidance on the regulatory and scientific aspects of the project, with joint health technology assessment advice as appropriate. The pilot project primarily expects marketing authorization holders to obtain regulatory approval for the new indication via a marketing authorization variation, in cooperation with the champions (65). The pilot project will be used to test the framework proposal, to learn from the practical applications of candidates and to build on the concepts defined. This will ultimately inform future EU steps towards facilitating repurposing of off-patent medicines for cancer.

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