Public funding of clinical research with societal return

Lydie Meheus, PhD
Managing Director @ the Anticancer Fund, Brussels, Belgium
November 15th 2019
Morningside CIAM, Emory, Atlanta
Public funding

Definition?

- **Comes from:**
  - Governmental money
  - Foundations (private & public)
  - Crowdfunding
  - Health Insurers
  - Companies (CSR)

- **Outcome:**
  - No (monetary) ROI
  - Serves the public (health)
Societal return

For patients and governments

- added therapeutic value
  - the incremental “therapeutic value” brought by a new drug or intervention compared with the best available treatment options already on the market (IP/A/ENVI/2014-17 June 2015 PE 542.219).
  - Overall survival of at least 4-6 months (“Pricing of cancer medicines and its impacts” Geneva: World Health Organization; 2018)
  - Quality of Life

- unmet needs: rare cancers
- Affordability/accessibility
Why is public funding a necessity?

Current “private” system focuses on ROI first
Need for a complementary “public” development pathway
Cancer treatment development drivers

- **Academic research**
  - Novelty
  - IP
  - Publication

- **Spin-out or spin-off**
  - Biotech
  - $$$

- **Registered drug**
  - Pharma
  - Create shareholder value
Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13

Courtney Davis,1 Huseyn Naci,2 Evrim Gurpinar,2 Elita Poplavska,3 Ashlyn Pinto,2 Ajay Aggarwal1,4,5

- 68 indications with EMA approval
- 51% showed sign of improvement in survival and quality of life
- 5 year follow-up
- Magnitude of benefit of overall survival = 2.7 months
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<th>Agent/Classification</th>
<th>Approval Date</th>
<th>Enrolled, No.</th>
<th>Cancer Indication</th>
<th>GMR, No.</th>
<th>Would Have Met ASCO Criteria?</th>
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<td>Second-line IL-2-target type, EGRF expressing CRC</td>
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**Special Communication**

**Unintended Consequences of Expensive Cancer Therapeutics—The Pursuit of Marginal Indications and a Me-Too Mentality That Stifles Innovation and Creativity**

The John Conley Lecture

Tito Rege, M.D., PhD, Shari Maitland-Kelly, M.D.; Andrew Lu, Ph.D.

JAMA Otolaryngology–Head & Neck Surgery December 2014 Volume 140, Number 12
Let's be honest – our research centres on drugs not patients

Precision oncology is about understanding what is driving an individual’s cancer growth, resistance and metastasis, and then targeting those pathways accordingly. Our current research models are good at developing drugs to hit targets. They are bad at learning about which targets need hitting in which patients and how best to do that.

A truly patient-centred approach would not involve just adding the expression of a target of interest as an inclusion criterion to a given trial protocol. That is an inefficient and wasteful way of finding the right therapy for each patient, as it would have to be repeated time and again until the drug–target match is found – if it is eventually found. In addition, scarce biological materials are usually lost in commercially siloed biobanks, and no one addresses treatment questions for those patients who do not express the target.

These are outdated research models, which

Putting the patient at the centre would require replacing the process by which trial protocols seek access to the patients they need, by a process that helps patients get access to the latest science that could help them. Such a process would start with systematic screening of every newly diagnosed patient and the biology of their disease. It would follow the patient through the course of the disease, providing longitudinal clinically annotated bio-collection, addressing tumour heterogeneity and the challenges of recurrence. This process would give patients the best chance to be matched with the best treatment for them, including via access to regulatory trials. Questions about treatment duration, combinations and sequences could be addressed by independent research.

Clinical research and healthcare models are long overdue for transformation. Systems need to be re-engineered to place patients at the centre.
Where is public clinical research required?

DEVELOPMENT
➢ (generic) drug repurposing
➢ Autologous cell therapy

ACCESS
➢ Registration trials, pivotal trials
➢ De-escalation trials, therapy optimisation trials
➢ Cancer registries, real-world data
A good example: The Netherlands

Identify where non-commercial drug development is desirable

Drug rediscovery, cell and gene therapy
Hard repurposing: build on of the increasing knowledge of the tumor biology ⇒ Microenvironment: immunological, metabolic, inflammatory pathways

Soft repurposing: unmet needs in rare cancers, especially paediatric oncology

“Efforts to eliminate cancers may actually hasten the emergence of resistance and tumour recurrence.”

A change of strategy in the war on cancer

Patients and politicians anxiously await and increasingly demand a ‘cure’ for cancer. But trying to control the disease may prove a better plan than striving to cure it, says Robert A. Gatenby.
Rebranding cannot be combined with label extension; Both philanthropic and governmentally-funded development; One additional year of market exclusivity if new indication is registered in first 8 years and brings significant clinical benefit over existing therapies; Currently, label extension can only be obtained by the market authorisation holder, label extension by third parties is not yet an option in the EU legal framework; Public promotion: adoption in clinical guidelines, communication with HTA and national reimbursement bodies.
Due to this lack of monetary incentive, “generic drugs found to work for a new disease are in a state of purgatory,” says Wegner. Indeed, no generic drug has ever been approved for a new indication by a manufacturer without modification of the drug’s delivery or its dose, which would provide renewed patent protection. Someone needs to step up to help move preliminary findings about these cheap and available drugs into the clinic where they can help patients, Wegner adds. “This is where foundations, advocacy groups, and the NIH can play a huge role.”

Craig Wegner, Astra Zeneca
What should change?

Collaboration between government and philanthropy: “public”

Adapt the regulatory/legal system (EU, US)
On June 19, 2019, Senate health committee Chairman Lamar Alexander (R-Tenn.) and Ranking Member Patty Murray (D-Wash.) introduced S.1895, the Lower Health Care Costs Act of 2019, including Section 213 titled "Modernizing the labeling of certain generic drugs." Section 213 of S. 1895 addresses the public health issue of outdated labels identified by Friends work as well as the previously introduced MODERN Labeling Act.
Outdated Prescription Drug Labeling: How FDA-Approved Prescribing Information Lags Behind Real-World Clinical Practice

Michael B. Shea, BA1, Mark Stewart, PhD2, Hugo Van Dyke, MS3, Linda Ostermann, BA1, Jeff Allen, PhD1, and Ellen Sigal, PhD1

Abstract
Background. Prescription drug labeling is an authoritative source of information that guides the safe and effective use of approved medications. In many instances, however, labeling may fail to be updated at new information about drug efficacy emerges in the postmarket setting. When labeling becomes outdated, it loses its value for prescribers and undermines a core part of the FDA’s mission to communicate accurate and reliable information to patients and physicians. Methods. We compared the number of drugs used indicated on product labels to the number of uses contained in a leading drug compendium for 43 cancer drugs approved between 1999 and 2011. We defined a “well-accepted off-label use” of a drug as one that was not approved by the FDA and received a category 1 or 2A evidence grade. Results of the 43 drugs reviewed in this study, 34 (79%) had at least one well-accepted off-label use. In total, 253 off-label uses were identified: 91 were well accepted, and 65% were used in cancer types not previously represented on labeling. Of cancer drugs, had more well-accepted off-label uses than brand-name drugs, on average (mean 1.37 vs 3.8, P = 0.01). Conclusion. The labeling for many cancer drugs, particularly for older drugs, is outdated. Although FDA-approved labeling can never be fully aligned with real-world clinical practice, steps should be taken to better align the two when high-quality data exist. Such steps, if taken, will assist patients and prescribers in discerning which uses of drugs are supported by the highest quality evidence.

Keywords
FDA, labeling, off-label use, compendia, postmarket evidence

Introduction
Each time a new drug is approved for marketing in the United States, an accompanying collection of drug-related information, called “labeling,” is made available to health care practitioners to inform safe and effective prescribing. Federal regulations state that labeling must contain a summary of the essential scientific information about a drug, and that the information contained therein must be informative and accurate.1 The content of labeling is written by drug manufacturers, but must be approved by the Food and Drug Administration (FDA) to ensure that it meets standards laid out in regulations. Labeling is a crucial source of useful information about prescription drugs, but it can also become outdated if new evidence of drug effectiveness is not submitted to the FDA in a timely manner. Most often, labeling becomes outdated when high-quality scientific evidence is generated that supports a new use of a drug, but the drug’s manufacturer does not file a supplemental application request for the new use to be added to the drug’s labeling. This may occur because the manufacturer did not sponsor the research investigating the new use, or because the manufacturer lacked sufficient incentives to generate a labeling expansion. Drug manufacturers are not required by law to update their products’ labeling with new uses, though they may choose to do so voluntarily when they wish to market their products in new settings.2

Uses of drugs in patient populations or for indications that differ from those prescribed on labeling are referred to as “off-label” uses. Off-label use in oncology is common; it has been estimated that more than half of all uses of cancer drugs are beyond the scope of approved labeling.3 The fact that a particular use is off-label does not preclude it from being incorporated into routine practice and covered by insurers. A policy dating back to 1993 requires Medicare to cover off-label cancer drug uses that have been deemed medically accepted by at least

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Supplemental NDA 21CFR314.70 ((b)(2)(v)(A))
“(c) SELECTION OF DRUGS FOR UPDATING.—If the Secretary determines, with respect to a covered drug, that the available evidence is sufficient to meet the standards under section 505 for adding information to the labeling or modifying information in the labeling regarding the use of the covered drug, the Secretary may initiate the process under subsection (d).
Dear Mrs Meheus,

Subject: Cancer research - Your email dated 30 November 2015

I refer to your above mentioned email to Commissioner Thyssen, which has been forwarded to Commissioner Andriukaitis. He asked me to provide you with an answer.

Despite some progress in recent years in the fight against cancer, this disease remains a key public health concern. The European Commission has been supporting the fight against cancer for over 30 years with a wide range of actions. This includes collaborative research, public-private partnerships and coordination of national cancer research efforts.

Many different stakeholders are active in this field, including organisations such as yours that support independent research. Their contribution is highly valued.

I agree with you that it is necessary that advances in the laboratory and new scientific findings are translated in actual treatment options that are available to concerned patients. In case of medicinal products this will require a marketing authorisation in accordance with the currently applicable standards. Those standards are necessary to ensure the quality, safety and efficacy of products that are used by patients in the European Union.

The submission of marketing authorisations or of applications for new indications is however, company driven. The competent authorities cannot extend the scope of a marketing authorisation on their own initiative. This being said, the EU legal framework contains provisions that incentivise line extensions of well-known substances. Moreover, new combination products, even if based on well-known substances, may benefit from market protection periods, which are intended to allow companies to recuperate their investment.
Regulatory Changes needed

Repurposing candidate
- Well-known, authorised compound
- Good toxicology
- High level of evidence of anticancer activity

Need for policy actions
Clarify regulatory pathways for development of repurposed drugs and facilitate patient access to treatments

Preclinical research / data
Clinical research Evaluated by EMA

Novel anticancer therapies
- Authorisation (EMA)
- Reimbursement (HTA)
- Clinical adoption (guidelines)

Off-label use

STAMP
(Safe and Timely Access to Medicinal Products expert group within DG Santé B5):
Approved proposal for a framework to support not-for-profit organisations in drug repurposing within the current legislation through Scientific Advice (SA)
‘Champions’ To Lead European Drug Repurposing Project

Executive Summary

Work is under way on a new European procedure to repurpose drugs. It would mainly be used for active substances whose authorization holder and the relevant data were granted by the EMA.

Cross purposes

“Repurposing” off-patent drugs offers big hopes of new treatments

EU ‘Repurposing’ Project Plans Pilot Phase

05 Mar 2019 | NEWS
Repurposing Off-Patent Drugs: Research & Regulatory Challenges

Picking a new therapeutic use for an existing drug seems like a simple way to get more treatments to more patients more quickly. However, finding new uses for drugs that are off-patent is like navigating through a sea of obstacles without an outrigger. No single entity owns the territory the obstacles are in. It is difficult to see the full scope of individual challenges, to prioritize which challenges are addressable, and to choose the most effective vehicle to navigate the challenges.

Join us for a free workshop on December 5-6, 2019. First, we will map out the challenges to repurposing drugs that are already on the market but lack commercial and regulatory incentives for research and development. Then, we will host interactive work sessions focused on exploring possible solutions to solve questions:

- Which problems impede progress the most?
- What are the possible solutions?
- Are there unprecedented problems with the proposed solutions?
- Which solutions can be implemented in the short term?
- Who owns the individual challenges?
- What challenges are shared space, and how do we establish a collaboration to address challenges faster?

Potential discussion topics

- Accessing existing data
- Identifying appropriate comparators
- Regulatory approval
- Drug labeling
- Health economics
- Payor perspectives
- Real-world evidence & real-world data challenges
- Historical attempts to fix similar problems

Who should attend

- Patients
- Philanthropists
- Non-governmental organizations
- Academics
- Pharmaceutical developers & manufacturers
- Healthcare economists
- Intellectual property lawyers
- Regulatory policy experts
- Computational scientists
- Payors & Payers

Download preliminary agenda
“As a society we need to ensure that we do not leave any reasonable opportunity for anticancer treatment untapped”
US: Dietary supplements: not regulated for safety and efficacy under the DSHEA of 1994

- More than 3000 patients randomized
- Antioxidant vitamins C and E, lutein, zeaxanthin, and zinc and cupper (specific dosing)
  - Investigation of 11 products from 5 top-selling brands making claims on vision and eye health
  - Claims are made for primary prevention: unproven
  - 4 products: lower doses
  - 4 products: additional compounds

Europe (EFSA) Food Supplements directive

Directive 2002/46/EC:

Article 6

1. For the purposes of Article 5(1) of Directive 2000/13/EC, the name under which products covered by this Directive are sold shall be ‘food supplement’.

2. The labelling, presentation and advertising must not attribute to food supplements the property of preventing, treating or curing a human disease, or refer to such properties
Conclusion

• Public funding is essential in a health system that centres on patient benefit.
• Valuable treatment options are not developed if there is no monetary incentive for the private sector to invest in the trials.
• Public funding is required not only for development of innovative treatments neglected by pharma but also to make these therapies accessible (on-label drugs) and affordable for all patients.
Thanks to the ACF team. Thank you for your attention. Any questions?
“Never doubt that a small group of thoughtful, committed, citizens can change the world. Indeed, it is the only thing that ever has.”

— Margaret Mead
Back-up slides
Study quantifies impact of NCI-sponsored trials on clinical cancer care

Posted: September 18, 2019

A new study shows that nearly half of phase 3 cancer clinical trials carried out by the National Cancer Institute (NCI)-sponsored SWOG Cancer Research Network, one of five groups in NCI’s National Clinical Trials Network (NCTN), were associated with clinical care guidelines or new drug approvals. NCI is part of the National Institutes of Health.

The analysis was published in JAMA Network Open® and conducted by researchers affiliated with SWOG from several institutions around the country. The study suggests that NCTN trials add value regardless of whether findings were positive or negative. In addition, the authors calculated the cost of running NCTN trials, and they also found that the cost of a U.S. Food and Drug Administration (FDA) approval from an NCTN trial was much less than the cost of an FDA approval from a trial run by pharmaceutical companies.

“We found that the NCTN program contributes clinically meaningful, cost-effective evidence to guide care of cancer patients,” said Joseph Unger, Ph.D., a health services researcher and biostatistician for SWOG at the Fred.

45%

OF 182 PHASE 3 CLINICAL TRIALS
BETWEEN 1980 AND 2017
INFLUENCED GUIDELINE CARE OR NEW DRUG APPROVALS

A study shows that 82 of 182 phase 3 clinical trials led by SWOG or by other NCTN groups with SWOG participation were “practiceto influential.”

Contact: NCI Press Office
240-760-6600
Lung Cancer Survival Gains:
Contributions of Academia and Industry

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Non-small cell lung cancer (NSCLC) is the leading cause of cancer death worldwide. Although overall survival rates among patients with the disease remain low, modest improvements have been reported in recent decades. These improvements have been achieved in large part due to practice-changing randomized controlled trials (RCTs), some related to drug products and others to interventions such as surgery and radiotherapy. Understanding which interventions have yielded overall survival gains and which institutional contributors have contributed to the RCTs realizing these benefits can help identify the key drivers of public health benefit and inform the allocation of scarce health care resources. Accordingly, we reviewed the sponsorship and funding of RCTs demonstrating life-saving outcomes in non-small cell lung cancer.

We used the National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (v.3.2017) to identify the cohort of interventions for this study. We chose the NCCN guidelines because they are the most widely used multi-disciplinary guidelines in cancer and include drug and non-drug interventions. For each intervention, we assessed its supporting evidence, selecting only interventions that were tested in at least one RCT. We collected the report of the RCT from PubMed and evaluated whether it found overall survival gains related to the intervention. Interventions for which RCTs did not find overall survival gains were categorized as taking place in the curative (non-metastatic) or non-curative (advanced or metastatic) setting. For each RCT, we recorded the overall survival gains (5-year overall survival rates were available in the curative setting and median overall survival was available in the non-curative setting; hazard ratios or other results were obtained for each setting), the sponsor (defined as the parent or entity that has responsibility for a clinical investigation), and the funder (defined as the organization providing financial support for the study). We categorized sponsors into industry, academia, or both, and funders into industry, public, or miscellaneous. When this information was not available from the published literature, we searched ClinicalTrials.gov; if unavailable, we contacted the corresponding authors. Results were analyzed descriptively.

Among 27 NCCN-recommended interventions, 19 (68%) were based on at least one RCT. Of which, 19 (49%) showed an improvement in overall survival in 26 RCTs published between 1990 and 2017 (Table). These 19 interventions included the same drug in different settings (e.g., pemetrexed as first-line and second-line treatment). Combining these, there were 17 distinct interventions.

While reaffirming the important contribution that industry makes in funding RCTs for developing new drugs to treat advanced disease, these findings also reveal the critical role that academic groups and public funding plays in identifying interventions that yield the biggest public health benefits, highlighting the value of continued public funding and support of academic trials.