Personalised Cancer Medicine Program

at Karolinska Institutet

Report on clinical effectiveness

Investigation by

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Important abbreviations

CEss	**Clinical Effectiveness**: Effect of an intervention in clinical practice in medical and health care for real health benefit - like symptom relief, recovery, or survival. To find out if something really works, all effects need to be studied; possible harms as well as possible benefits.
CEy	**Clinical Efficacy**: Effect of an intervention in a clinical study. Strict inclusion- exclusion criteria providing selected patient groups, and treatment given under strict controlled conditions, often in comparison to established treatment.
CEcy	**Clinical efficiency**: The clinical production of the desired effects or results with minimum waste of time, money, effort, or skill. A measure of clinical effectiveness; specifically is the useful work output divided by the energy input.
OR	**Outcomes Research**: Clinical and population based research that seek to optimize the end results of healthcare in terms of benefits to the patient and society to identify shortfalls in practice and to develop strategies to improve care.

Summary

This is a report on aspects of **Clinical Effectiveness (CEss)** in relation to the **Personalised Cancer Medicine (PCM)** research program at Karolinska Institutet (KI).
CEss research study effects of interventions in clinical practice (real-world effects). The obtained data provide important additional information to results from clinical trials (clinical efficacy, CEy). In CEy patient populations are relatively homogenous and treated under controlled conditions. **Outcomes research (OR)** includes all aspects of CEss as well as costs and resources (end-result); outside the scope of this report.

As compared to Clinical Studies, CEy (homogenous patients treated under controlled conditions), CEss studies with a biological approach (**biological-CEss**) inform on wider biological aspects affecting treatment effects (heterogeneous patient groups treated in clinical practice) can provide increased understanding of side-effects, and may better sub-group patients. Furthermore, studies with a biological-CEss approach are only feasible in very few countries (Nordic countries, The Netherlands, the UK), as these countries have population based cancer registers, making it possible to identify all patients in a certain population.

New innovative cancer drugs are increasingly developed for small and targeted patient populations, and therefore many cancer drugs have orphan drug status, meaning that the drugs were approved based on limited data on few patients. New cancer drugs are also taking up an increasing share of the cancer health care budgets. This contributes to the importance of defining which patient benefits the most from each treatment, and hence CEss studies can be very useful.

The aim of this report is to provide an overview of CEss aspects in order to identify areas where the PCM-program at KI can facilitate CEss research in Stockholm. The overarching questions: What can be achieved by using a biological-CEss approach in PCM research? What changes or improvements are required?

CEss research comprises several challenges:

- Level of evidence with CEss studies related to established methods
- Common view of disease management
- Infrastructure for data collation
- National and international competing initiatives

There are numerous efforts in the CEss research field today, both in Sweden and internationally. These efforts use different approaches and different methods. In Stockholm, as well as elsewhere in Sweden there is little coordination and collaboration in relation to PCM research, and the initiatives result in a fragmented research environment often with doubling of efforts.

The suggestion for the PCM program, in relation to CEss, is to contribute to the formation of a structure for establishing the role of CEss as a key component in the total translational research process. The actions will need to focus on short-term, medium-term, and long-term perspectives. In the short-term the focus is awareness, training, and education, the medium-term should focus on study set-ups and collaborations. This could best be achieved within the existing structure of clinical studies. The long-term would need to focus on creating sustainable infrastructures for biological-CEss research.

The competitive research environment in Sweden does not encourage collaboration efforts. If the PCM program can establish a true translational/PCM infrastructure at KI and in Stockholm, faster (better?) results will be achieved, providing faster improvements in cancer care.

In summary, CEss research can be used

- to define subgroups of patients in a heterogeneous population
- for longitudinal healthcare databases
- to analyse large health care databases
- as ethical basis for the practice of health care
- for improvement in the quality of care
- for medical informatics
- for implementation research in health care
- as a basis for decision making in health care
- for decision analyses in health care

Introduction

The Personalised Cancer Medicine, PCM program at Karolinska Institutet (KI) is a research-based initiative for the implementation of modern precision cancer medicine. The purpose of the program is to facilitate PCM-related cancer research, aiming at improved cancer management in clinical routine practice, achieved by catalysing synergies between existing and developing research and health care. The information for this report has been compiled from my own research experience, discussions and presentations at meetings, etc., and collected from different official web sites, as well as written/oral communication with scientists, clinicians and administrators at KI and Karolinska University Hospital (KS), as well as elsewhere.

This report focuses on aspects of **Clinical Effectiveness (CEss)** in the PCM program. CEss means the total effect of an intervention in clinical practice (real-world effects), including all aspects of patient care (also patient reported outcomes measures, PROM), in contrast to results in **Clinical Studies (Clinical Efficacy, CEy)** where patients are treated under controlled conditions**.** CEss includes all data for all treated patients in a certain population, and not a selected sample, as in CEy. Data collected for CEss should include all treatment and patient related aspects as diagnosis, medical history, treatments, schedules, dose reductions, side-effects, etc. One important aim of CEss research is to study all interventions to be able to define best practices. **Outcomes Research (OR)** focuses on end-results in health care, also resources and cost. OR is mainly used for health policy considerations, and decisions on priorities, and is a research field in itself.

The area of CEss/OR is complex, multidisciplinary, and requires input from several different stakeholders. These are mainly; Patients, Authorities, Health Care Providers, and Pharmaceutical Industry.

“Outcomes Research focuses on end-results in health care, including all aspects of Clinical Effectiveness, also resources and cost.”

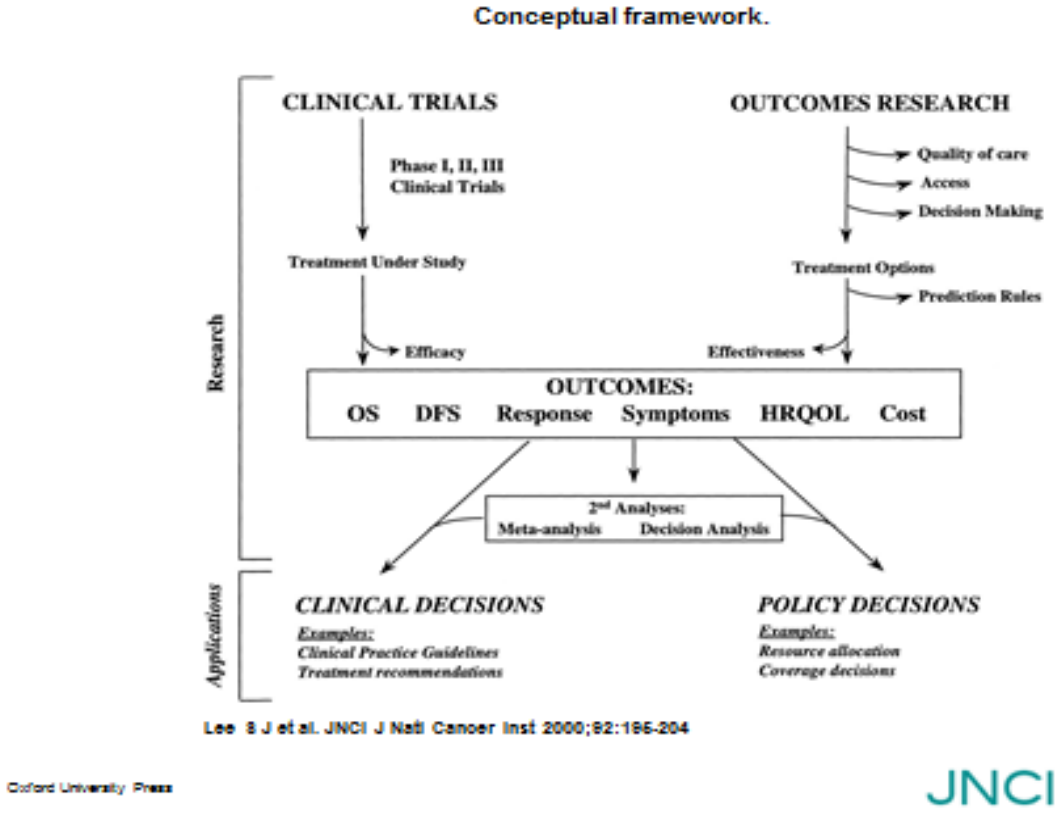

Figure 1 Overview of clinical trials versus outcomes research [1]
Clinical trials include patients with strict inclusion- and exclusion criteria, and patients are treated under controlled conditions. Results from these studies inform on efficacy, and they are often used for the development of clinical guidelines. Outcomes research includes all patients treated in clinical practice. These studies include all aspects affecting the delivery of care, and are often used for policy decisions. Clinical effectiveness studies are part of the total outcomes research field and focus on effects of interventions in clinical practice (use of real-world data) and, hence patient groups are heterogeneous. This will allow for studies on patient groups outside of clinical studies, as well as development of quality of care.

CEss may provide accelerated opportunities in the research community—particularly improving the targeting, tailoring, sequencing of different approaches to develop a complete set of evidence for the translational research process. Enhancing the use of genomic information in CEss (**biological-CEss**) can accelerate the timeliness and level of research. As there are many interventions and treatment options in oncology -with great complexity- effects of use in clinical practice provide data not possible to collect in controlled clinical studies. Information from patients treated in clinical practice may also provide genomic information for further translational studies and thereby improve patient selection (e.g. new indications, extended indication), see figure 4.

The drug development process, in the area of medical oncology, has become complex, time consuming and costly both for the pharma industry and for health care systems. New drugs are increasingly

developed for small patient populations, and many cancer drugs have orphan drug status (prevalence ≤ 5 patients/ 10,000 inh). Some drugs have conditional approval, requiring additional post-approval data [2]. In 2015, 11 non-targeted oncologic orphan drugs, and 15 targeted oncologic orphan drugs were approved by EMA [2]. Thus, a great number of drugs are approved based on very limited data on few patients under very controlled conditions, emphasising the need for continued studies after drug approval. See also figure 2. In summary, the importance of CEss research in medical oncology is increasing.

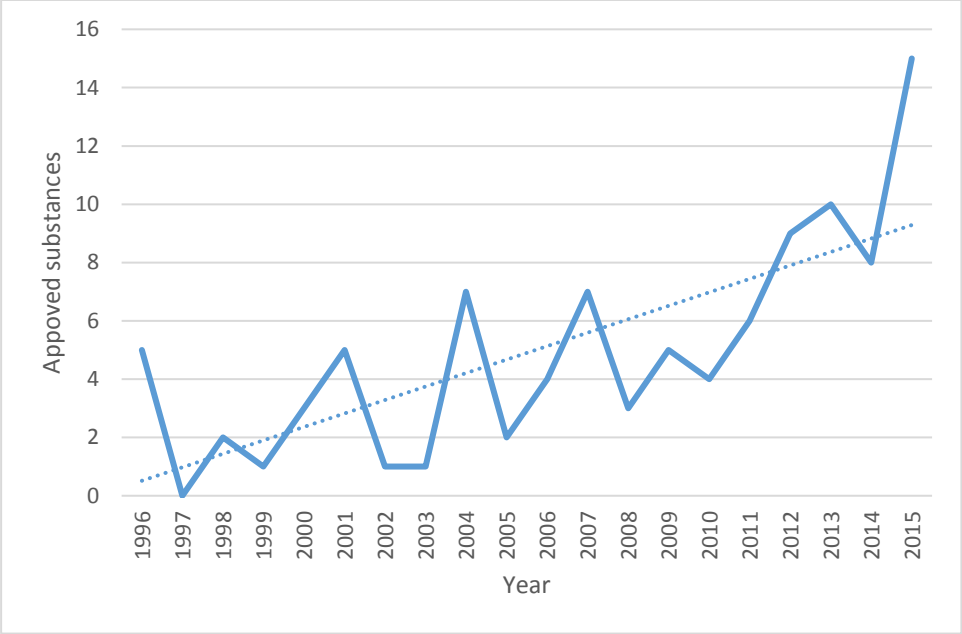

Figure 2. The number of approved oncology drugs has increased rapidly [3]. In the 1990-ies only few drugs were approved (mainly cytotoxic drugs). During later years 5-15 drugs have been approved each year, putting great economic pressure to health care systems.

Health economics and clinical effectiveness

In 2014, the countries in the European Union spent EUR 19.1 billion on cancer drugs compared to EUR 9.1 billion in 2005 (Figure 3). The drugs´ share of the total oncology health care cost has doubled during the same period. Sweden is among the higher spenders on cancer care, with EUR 219 per capita. In total Sweden spends EUR 3,213 per capita on health care; less than 10% on cancer care [3].

Health economic studies are important as a basis for resource allocation in health care systems [4, 5], reflecting the limited resources available in health care systems [6]. Health economic studies has developed over many decades and should really include all aspects of the intervention (e.g. demographics, disease panoramas, treatment efficacy, effectiveness variation in health practices, cost-effectiveness, social and ethical aspects), to be able to define the value of a specific intervention [7, 8].

It is also important that health economic studies are made relevant for the country or the situation, as health care systems differ [9]. One important aspect in assessing value is the perspective on cost, as there is no documented relationship between cost and effect of drugs in oncology. At the same time, usage of new cancer drugs result in a statically significant reduced mortality and can be of good value to society [10-12]. In general, investments in health care are of good value for money, especially investments in breast cancer. An interesting example is the anti-hormonal drug tamoxifen used to treat hormone sensitive breast cancer. In the early days of usage, in the 1980-ies, tamoxifen was regarded as very expensive with limited effects. Now we know that tamoxifen treatment has been very important for the increased survival in breast cancer [13]. After 25 years of follow-up in Sweden the return on investment of tamoxifen use in breast cancer is SEK 25 per invested SEK [10, 14]. As more treatments in oncology receive an orphan drug status it is important, also in this group of drugs, to define the value of each treatment, and not only look at the cost [15-17].

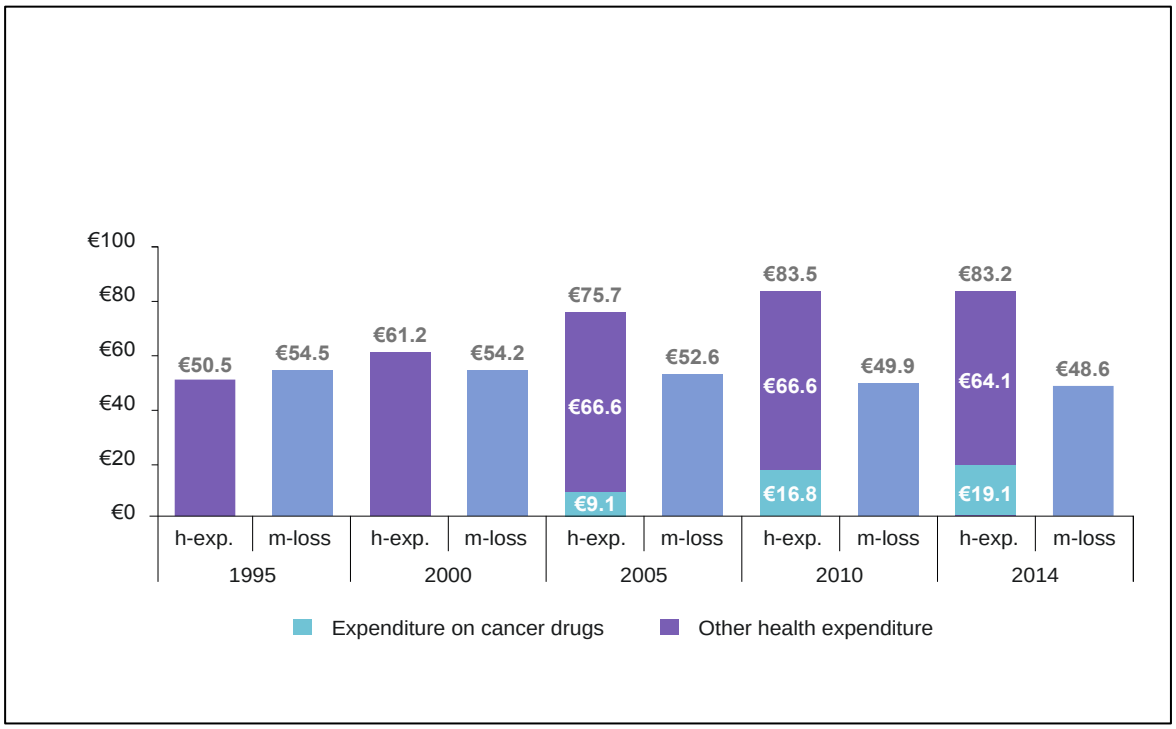

Figure 3. Changes in the composition of total cancer costs in the EU (billion Euros in 2014 prices) [18]. Premature mortality has decreased over time. Health care expenditure on cancer has been relatively stable since 2005. Drug costs have doubled during the same time period, although the cost of cancer drugs constitutes of around 1% of total health care expenditure. EU = European Union; h-exp = health expenditure on cancer; m-loss = production loss due to premature mortality from cancer during working age.

Quality Adjusted Life Years

Quality Adjusted Life Year (QALY) is a measure of disease burden, including both the quality and the quantity of life lived [19]. In health economics it is used to assess the value for money of an intervention [20].

The advantages of using QALY as the outcome measure is that it can combine different consequences into one measure, making comparisons possible between interventions affecting Quality of Life (QoL) with interventions affecting survival (Life Years Gained, LYG). The acceptance of QALY differs and is not always useful, and LYG estimation may be sufficient in cancer as it correspond well to QALY [21]. There are also several ongoing efforts in finding other measure scales in oncology (ESMO, ASCO, etc). The European scale from European Society of Medical Oncology (ESMO) is a validated and reproducible tool - the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) – made to assess the magnitude of clinical benefit for cancer medicines [22]. The American Society of Clinical Oncology (ASCO) is developing a value framework for assessing the value of a particular cancer treatment [23].

Willingness to pay

In economics, the willingness to pay (WTP) is the maximum amount a person/society would be willing to pay, sacrifice or exchange in order to receive a benefit or to avoid something undesired.

The more society is willing to pay for improvements in health, the more society is willing to pay for interventions that will improve health. An intervention will not be adopted if the WTP per QALY gained/LYG is not at an acceptable level [24].

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Why are Clinical Effectiveness studies important?

CEss studies use data collected from patients treated in clinical practice, and should have the total aimed patient population as the basis. The advantage of CEss results is that these can inform on many aspects of care, from genomics to quality of care, and guide decisions on patient access to an intervention. CEss studies with a biological approach (**biological-CEss**) may inform on aspects affecting treatment effects (e.g. co-morbidities, with or without treatment). Biological-CEss studies may be useful in studying genomic aspects in a patient population to learn more about which genomic features correspond to response, side-effects, or other factors affecting patients' outcome. Furthermore, studies with a biological-CEss approach are only feasible in very few countries (Nordic countries, The Netherlands, the UK), as these have population based cancer registers, and relatively comprehensive data collection [25]. CEss studies are also important as controlled clinical trials (CEy) recruit patients who are relatively young, have less co-morbidity and are treated and followed within a highly specialised clinical setting. To be able to carry out studies on CEss patient access to the intervention is required, and it is crucial to have systematic information on all interventions, drugs, and treatments provided to patients. In Sweden there are, since 2005, complete data on prescription drugs and many hospitals register usage of hospital drugs, as well as other treatments and interventions provided.

The entire OR area covers the totality of end-results in healthcare (i.e. effects and total resource use and costs); areas outside of the scope of this report. The focus of this report is usage of CEss studies in the PCM research program at KI; existing conditions, strengths and weaknesses, as well as strengths-weaknesses in relation to other regions in Sweden and outside of Sweden.

The overarching questions are: What can be achieved by using a biological-CEss approach in personalized cancer medicine (PCM) research? What focuses, changes, adjustments, improvements are required to make best use of CEss studies within in the PCM program?

Focus on clinical effectiveness studies

Without CEss studies true PCM research cannot be achieved (see figure 4), as data from patients in clinical studies will not suffice. Patients in clinical studies are more homogenous/less heterogeneous compared to patients in clinical practice, and hence, information on all relevant patients in a certain population is missing.

Today, there is a lot of attention to CEss in oncology. At the international level the attention is related to access to interventions, equity of care, data sharing, etc. Patient advocacy groups focus on access to care, equity of care, etc. Health care providers focus on access, quality of care, clinical efficiency (CEcy),

etc. Academia focuses on development and research opportunities. Authorities focus on safety, access to care, and health economics. Pharmaceutical industry focuses on innovations and market opportunities. All stakeholders will need to get involved at some point in the process for full functioning CEss research. Today this is difficult to achieve and coordination and collaboration require a lot of attention.

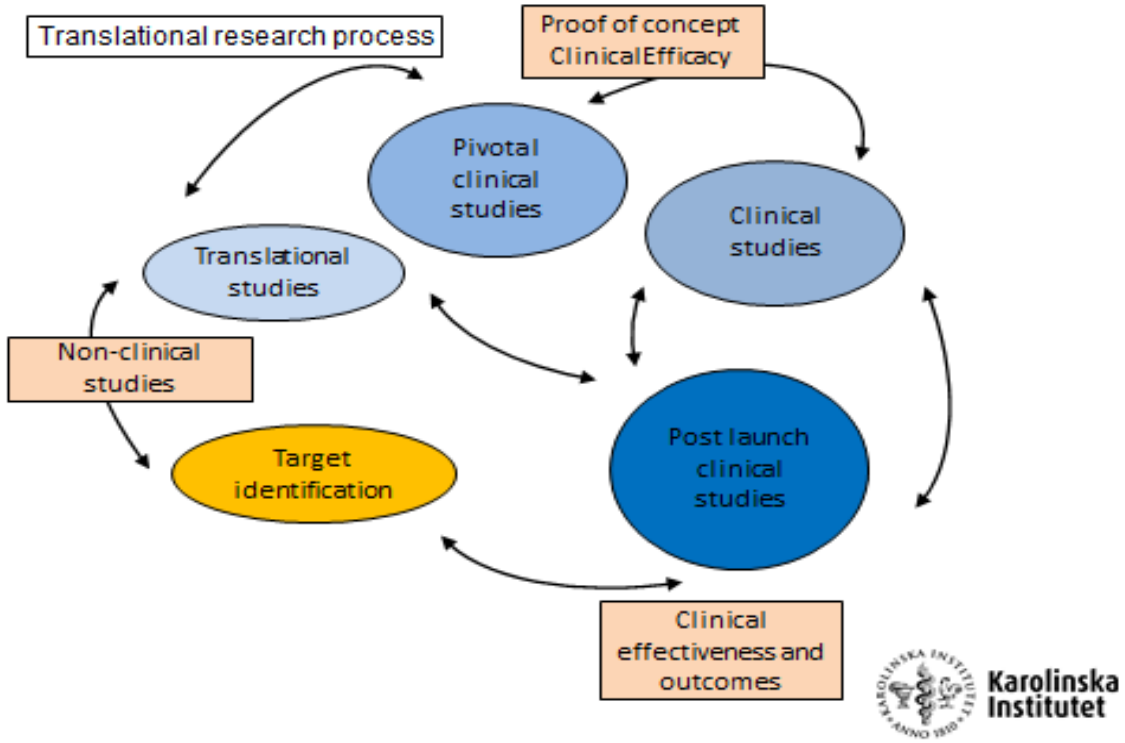

Figure 4 Schematic overview of the entire translational research process. Clinical Effectiveness studies can inform the translational research process, e.g. target identification, patient sub-groups, and treatment recommendations.

The headings below are categorised as

strength; meaning that it is well developed in Stockholm,

weakness; meaning that it is lacking in Stockholm, or

challenge; meaning that there is need for further focus/development and knowledge.

Stakeholders (challenge)

For CEss research, as well as for the total PCM program, there are several important stakeholders. These have different perspectives and motives for their efforts, and therefore it is crucial that each relevant stakeholder is included in related to steps of the translational process for PCM research. Organisation of cancer care is of great importance for improvements in outcome, and a fragmented situation for research will delay improvements as tasks may be doubled.

The stakeholders are at least the following:

- **Patients** are of course, the main stakeholders. Patients are generally interested in access to care, quality of care, and equity of care. Patients are also generally positive to new treatments and may accept even low clinical benefit. NB! Furthermore, older patients have same benefits as younger patients, and side-effects are not more difficult to manage. Patients have to consent to sampling and may need to consent to data collection. PROM data is also required for good quality CEss studies, and there are many validated questionnaires, both general and for different cancer diagnoses.
- **Health Care Providers** have the overall responsibility of delivery of care and are responsible for the budget for the delivery of care. **Health Care Workers** should follow current guidelines and systematically document data (e.g. as in clinical trials, separate report in the PCM program). If data is difficult to interpret, CEss studies will be less conclusive. **Registers** and other data sources collect data (should be systematically collected). **Biobanks** process and handle biological samples (separate report in the PCM program). **Adjacent facilities** carry out different analyses related to the disease (separate reports in the PCM program). **Basic- other researchers** compete for funding, thereby making collaboration challenging (separate report in the PCM program).
- **Authorities** approve drugs and other interventions as well as provide information on health economics of interventions. As mentioned before, many oncology drugs are approved of data on few patients. Thus, Authorities may require post approval data for safety and survival. Legal aspects of interventions are also important for Authorities.
- **Pharmaceutical Industry** market drugs/interventions, and their interest is generally related to drug development and today there is a focus on value based care. It is important to note that much data included in the current analyses is from the clinical studies, and not from patients in clinical practice.

The greatest challenges with the stakeholders are to achieve a good communication atmosphere, as well as to achieve a common understanding of the value of CEss research.

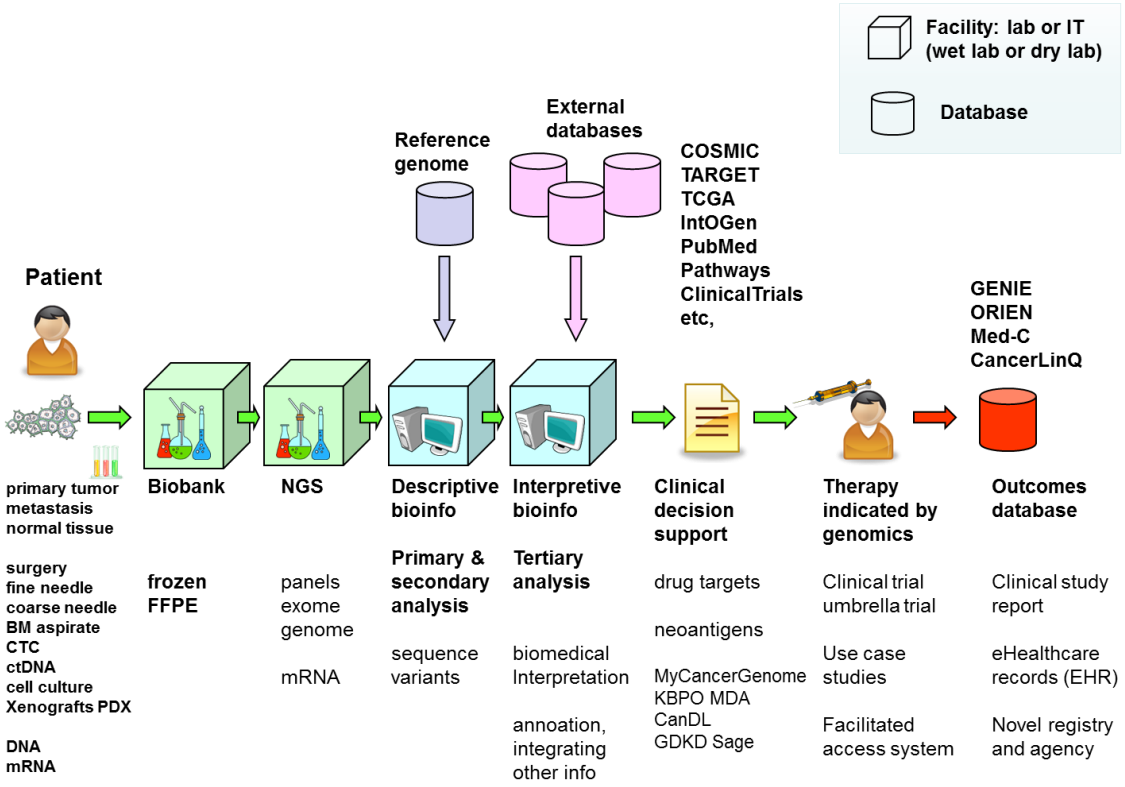

Figure 5 Detailed overview of the entire translational research process (from Anders Wennborg)
The translational research process includes many aspects of non-clinical research, as well as clinical research. All aspects need to connect to the other aspects and clear communication routes are required, as the interests by different stakeholders may differ.

Level of evidence of clinical effectiveness data (challenge)

According to the Swedish National Board of Health and Welfare (SoS) and the Swedish Agency for Health Technology Assessment and Assessment of Social services (SBU) the level of clinical evidence are ranked as follows (1 = highest level of evidence, 5 = lowest level of evidence):

1. randomised controlled studies
2. non-randomised studies with external control group
3. before-after measurements without control group
4. cause-effect studies
5. experts' opinion

CEss studies challenge these standard evidence levels. CEss studies provide information on “real world” use and practice which detect signals about the benefits and risks of use in the patient population. CEss studies:

1. help formulate hypotheses to be tested in subsequent experiments;
2. provide part of the community-level data needed to design more informative pragmatic clinical trials;
3. inform clinical practice [26, 27].

For example, there is data showing that results on progression free survival (PFS) in controlled clinical studies in oncology do not automatically translate to overall survival advantage [28-30].

Also, many drugs in oncology aim at small patient populations, and thus, data from controlled clinical studies may be limited and many aspects of the drugs may not be fully explored (i.e. overall survival, toxicity). These aspects require further attention with long-term follow-up on clinical outcome and storage of biological samples in biobanks and primary genome data to be able to study biological-CEss aspects (see Figure 6).

It is a challenge to collate data from clinical practice to an analysable format. There is also a clear lack of interest of sharing data. Furthermore, there are numerous confounders in clinical practice affecting the results; patient related aspects (e.g. co-morbidities, genetics) and treatment related aspects (e.g. treatment schedules, dose reductions, sequences, pre-treatments, other treatments), and this will decrease the number of patients in each sub-group, requiring collaboration between hospitals, regions and even countries [31]. This has important legal implications.
There is a current SBU report on usage of drugs in CEy-CEss, showing that we need to continue these discussions to establish the level of evidence of CEss studies [32].

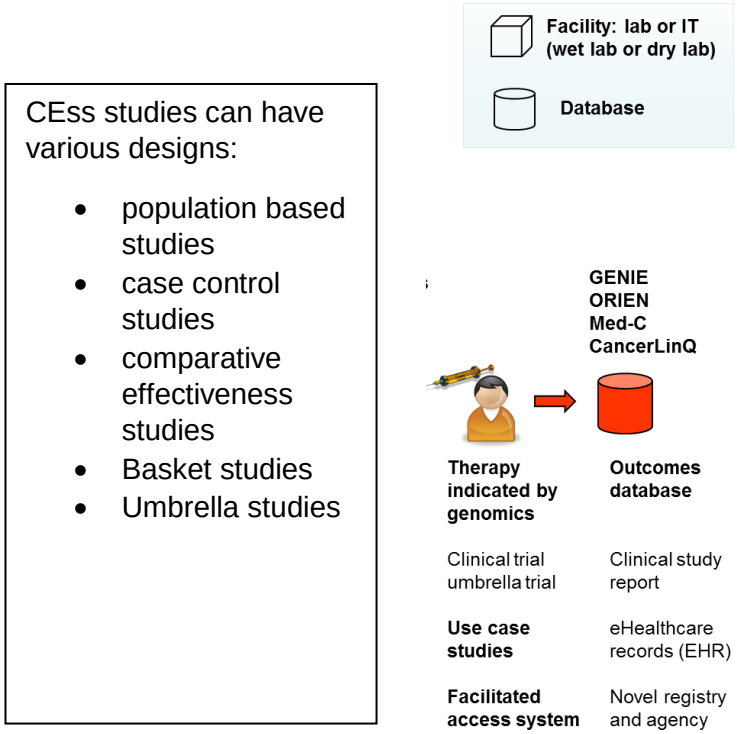

Figure 6 Clinical Effectiveness studies
Traditional CEss studies have had typical designs; population based studies (including all patients in given geographic area); case control studies (matched controls); comparative effectiveness studies (comparing two or more standard clinical interventions used in the same patients). In the future, there may be other designs for biological-CEss studies using patients/tumour biological specifics, and sub-group patients in a given therapeutic area, or comparing different therapeutic areas according to biological features (e.g. specific gene aberrations).

Cancer registers and data compilation for clinical effectiveness studies (strength/weakness)

In Sweden we have one of the world's longest traditions of collecting population based cancer data. Additionally, we have the unique opportunity to track all individuals in all registers, via a personal identification number (PIN), unique for each person living in Sweden. However, despite the long tradition of registers, fundamental data of treatment and follow-up data is still not collected. This is a weakness related to CEss research.

Today, there are initiatives in Stockholm, as well as elsewhere in Sweden related to systematic registration and collection of clinical data. The **4D project** and the **National Cancer Portal** are the two in the forefront in Stockholm. The 4D project (collaboration between the Stockholm county council and KI) includes arthritis, breast cancer, type 2 diabetes, and heart failure. The 4D has a separate project for informatics to enable the linkage of medical records, patient e-health accounts, quality registers and biobanks. The **National Cancer Portal** (a collaboration between the Regional Cancer Centres, RCCs) aims

at monitoring and follow-up of best usage of biomarkers for improvements in clinical practice [33, 34]. One interviewee in a central position at the Karolinska University Hospital said that the current local/National/International initiatives will improve data quality, quality assurance, quality control and research, although it requires some more work during some more years. There is also a lack of interest in data sharing (i.e. competition between research groups).

The HIV register in Sweden and the Stockholm melanoma group uses a commercial product (**RealQ®, Health Solutions,** also used by other centres in Sweden) for CEss studies. These registers are used for informed decisions in clinical practice, quality assurance, and research. Some data is automatically downloaded into the system, and some data is manually entered. The latest addition to the HIV register is to include PROM data.

In Sweden there are six RCCs. These should represent the patient within healthcare, to provide best and equal opportunities. In relation to research, RCCs should facilitate inclusion into clinical studies, including collaborations with the pharmaceutical industry. RCCs should make plans for clinical research (also in a broader sense) and innovation, and organize support functions. SoS published an audit report on the RCCs in 2015. In this report it was stated that there are a lot of research efforts by many actors, although there is no true overview and no coordination and also a lack of cooperation [35].

During my investigation I have found out that there is a common opinion that data capture for CEss studies has been slow, but improvements are now underway, both within Sweden and internationally. All the above initiatives have the same focus, i.e. improving data quality in clinical practice, and to make way for CEss studies. The challenges are mainly related to the lack of communication/coordination between initiatives.

It is also important to note that patients included in CEss studies may need to consent to data capture and compilation, and this is important to consider before designing any study. There is also the issue of ownership of data. According to Swedish practices the patient owns her/his data. According to Swedish Law (Patientdatalag 2008:355, 7 kap) register data can only be used for:

- Statistical analyses
- Research within Health Care
- Other legal reporting

Cancer register data has no ownership (patient has to consent), and research should be promoted, although it should be noted that projects should have ethics approval before initiation.

In order to achieve good data quality for CEss studies there should be collaborations between relevant stakeholders as well as a common understanding of the aims.

"There are a lot of research efforts by many actors, although there is no true overview and no coordination and also a lack of cooperation"
(Audit by National Board of Health and Welfare on organization of the Regional Cancer Centres)

Co-dependent technology and clinical effectiveness (weakness/challenge)

The increased knowledge of tumour biology has translated into increased use of agents targeting specific cellular pathways. Patient populations are increasingly defined by the presence or absence of different biomarkers, in addition to traditional tumour definitions. There are three major aspects to this:

1. The first is about test reliability. To be confidently used in medical decision-making, test methods must meet standards of statistical reliability, i.e. it must be accurate, precise, specific and sensitive.
2. The second is related to the optimal treatment strategy, taking into account outcomes in terms of survival and quality of life and side effects. These two aspects are not independent and the optimal testing and treatment strategies have to be analysed together.
3. The third, clinical utility, refers to whether the test can provide general genetic information useful for clinical decision-making in relation to diagnosis, treatment, management, and prevention of a disease.

Testing without treatment is meaningless unless a special value is assigned to the information about prognosis. Treatment can be undertaken without testing, but may provide unnecessary side-effects when patients with no or minor benefit are exposed to treatment. As patient populations are getting smaller, the knowledge gained from controlled clinical studies will be limited also in relation to the usage of co-dependent technologies.

Data collected from usage in clinical practice can provide additional knowledge on patient sub-populations (based on co-dependent analyses and genetics), as well as providing information relevant for further translational research.

The aspect of co-dependent technologies is a weakness today as testing is set up differently at laboratories, and comparisons may be difficult (NB! Quality Controls). The aspect of co-dependent technologies is also a challenge, as the testing has to provide a correct identification of patients, and good and comparable standards have to be developed for each testing method used. The challenges are also related to the acceptance of used standards.

National projects with a clinical effectiveness approach (strength/weakness/challenge)

In Southern Sweden (**SCAN-B**), and in Uppsala (**U-CAN**) there is an ongoing study project on gene expression in breast cancer tumours with the aim to screen all breast cancer patients for improved precision of interventions [36]. This is still a research project, but has the future aim of clinical practice applications.

Also, in the U-CAN project clinical data on breast cancer patients has been collected since late 2013, with the aim to carry out CEss analyses. Within this project there is a newly started additional project on the Fluorometric Microculture Cytotoxicity Assay (FMCA) with the aim to improve therapy selection for each individual patient [37].

There is an initiative on including Patient Reported Outcomes Measures (PROM) from Swedish Association of Local Authorities and Regions (SKL), called the PROM centre, with the aim to include PROMs to register data. There are already several cancer registers including PROM (a survey carried out by the PROM centre in 2014): (cancer register – evaluation forms used)

- Haematology register - Everyday cognition (ECog)
- Lung cancer register – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), Performance status
- Oesophageal and gastric cancer - EORTC-QLQ-C30 and EORTC-QLQ-OG25 (Oesophageal-Gastric)
- Liver- and gall bladder cancer register - EORTC-QLQ-C30 (in a project), ECog
- Pancreatic cancer - EORTC-QLQ-C30 and QLQ-PAN26 (Pancreas)
- Gynaecology-cancer register - Performance status
- Colorectal cancer - EORTC-QLQ-C30 and QLQ-CR29 (Colorectal Cancer) (in a pilot study)
- Head and Neck cancer - EORTC-QLQ-C30, EORTC-HN35 (Head and Neck), Hospital Anxiety and Depression Scale (HADS), Performance status (in a study)
- Kidney cancer - EORTC-QLQ-C30 (in a pilot study)

The long tradition of the registers in Sweden is a strength as well as the willingness to develop the data included in the registers. At the same time there are important weaknesses, as the different registers collect different data, and important data (e.g. co-morbidity, treatments and side effects) are lacking. The challenges include common views on data collection, as well as collaborations for effective processes.

International outlook (strength/challenge)

At the international level there are several initiatives and the challenge is related to collaboration efforts, as there are many differences between countries in terms of legal systems and also in terms of health care systems (lack of population based data).

The **CancerLinQ** initiative from the American Society of Oncology (ASCO) [38, 39] stands for "Learning Intelligence Network for Quality". The aim is to construct a rapidly learning health care IT system through the collection, aggregation and analysis of health care data, allowing real-time clinical decision support to facilitate treatment planning for specific patients (www.cancerlinq.org). In the US there are difficulties tracking patient data, as different systems identify individuals differently, and the aim is to use a joint identifier similar to the Swedish system [40]. The clear focus for 2020 for CancerLinQ is international collaboration for CEss studies and for clinical decisions. Sweden may be a country in the collaboration, as there are registers of all diagnosed cancer patients, and discussions are ongoing. An increasing number of patients in the system allows for more rapid data compilation, in order to provide informed decisions in clinical practice, as well as carrying out CEss studies.

The **International Consortium for Health Outcomes Measurement (ICHOM)** is an initiative aiming at standardizing procedures for disease diagnosis and follow-up. "ICHOM's mission is to unlock the potential of value-based health care by defining global Standard Sets of outcome measures that really matter to patients for the most relevant medical conditions and by driving adoption and reporting of these measures worldwide". KI has a central role in the ICHOM initiative, and cancer diagnoses are the first runner-up. KI has also an important position with the PROMs in breast cancer. The aim of the ICHOM initiative is to cover more than 50% of global disease burden in 2017. It is important that all countries use best efforts to follow the ICHOM routine to be able to standardize data collection at an international level and thus, make way for CEss studies [41].

The **Cancer Core Europe (CCE)** Initiative has several aims, sharing biological- and genomic data, clinical studies, education and training. Today there is a number of Comprehensive Cancer Centres (CCC) in

Europe [42]. Ultimately, the CCE initiative aims at establishing a pan-European virtual Cancer Centre comparable to the National Cancer Institute in the US. KI is one of the core centres in the initiative. The leader of CCE, Alexander Eggermont states that "Precision medicine needs to be one big project and we need to put an end to the fragmented data warehouses" [43].

A biological- CEss approach could be used for international data- banking of different tumour mutations, and this can be used to speed up studies on specific genetic aberrations [44].

"Precision medicine needs to be one big project and we need to put an end to the fragmented data warehouses"
(leader of Cancer Core Europe, Alexander Eggermont)

Suggested actions for the PCM program

The suggestion for the PCM program, in relation to CEss, is to contribute to the formation of a structure for establishing the role of CEss as a key component in the total translational research process. The actions is short-term, medium-term, and long-term, respectively. In the short-term the focus is awareness, training, and education, the medium-term should focus on study set-ups and collaborations. This could best be achieved within the existing structure of clinical studies. The long-term would need to focus on creating sustainable infrastructures for biological-CEss research.

In the shorter perspective the PCM program could be a point of CEss project initiation. This could be facilitated by using existing structures (clinical trial unit), and provide proactive communication between the different stakeholders by initiating forums and meetings.

The factors related to biological-CEss research, both in terms of the complexity, as well as to the several ongoing initiatives, are listed below:

- The level of evidence for CEss results
- Systematic data registration and compilation
- Collaboration between stakeholders
- The Swedish cancer registers provide not all relevant data

- Data sharing of biological data
- Several initiatives with a CEss approach, both within Sweden as well as internationally.

The fragmented situation in Stockholm (e.g. different efforts for data collection) requires efforts in relation to collaboration and coordination.

In the shorter perspective, the PCM program should aim at improving knowledge, best practices and development of data sharing and infrastructures.
In the longer perspective, the needs are related to collaboration between stakeholders and the creation of sustainable infrastructures, both in the translational process, as well as for data collation.

Facilitation of clinical effectiveness studies

CEss studies are central for the success of the PCM approach in the long run. A biological-CEss approach could be used to;

1. target patient sub-groups
2. study new methodology in early clinical studies and patients in clinical practice
3. share data on biology-CEss oriented patient sub-groups
4. identify best practices for biology-CEss.

Furthermore, biological-CEss studies challenge at least the following:

1. Level of evidence requirements, as biological-CEss results are not included in guidelines
2. Cancer diagnoses and biological similarities/differences; umbrella/basket CEss studies, as still few patient are selected for treatment based on this approach
3. Informed Consent requirements.

Pharmaceutical Industry collaboration

There is an interest in the biological-CEss approach from pharmaceutical companies. Most plausible explanation to this interest is the aim for better patient selection and improved delivery of care (i.e. define clinical efficiency, see abbreviations). This attention has resulted in initiatives from different research groups resulting in a fragmentation of CEss research and low grade of collaboration non-clinical/clinical research. Also, a biology-CEss approach may provide additional knowledge that could be used for further research, to improve treatment strategies, in terms of clinical efficacy, clinical effectiveness and clinical efficiency; the hurdles being resources, data sharing, drug usage and cost. The

PCM program may facilitate these discussions in collaboration with other stakeholders, and arrange meetings with researchers and industry representatives.

Collection of clinical data and biological data

Systematic collection of data on interventions and patients, as well as PROMs is essential in CEss. Creating infrastructures and simplified data capture processes will be central for the success of CEss studies. Data sharing is also important for the future and the PCM program may facilitate the connection and collaboration between stakeholders collecting real life clinical data, biological samples, as well as PROMs. The ongoing initiatives and registers with PROM data could be used to learn and to identify areas for improvement. Today, the PCM program can act for the development of infrastructures using experiences from clinical trial processes. The PCM program can also evaluate different systems and work with the different stakeholders.

Education and training

With the increased attention to the CEss field, it is important to increase awareness and competence among stakeholders. The progressive introduction of genomic data in clinical settings, multidisciplinary tumour boards and information to patients, also leads to requests for CEss results. As mentioned earlier in this report, there are several efforts made to improve data quality at the clinical level. To implement these initiatives training programs on systematic data registration needs to be implemented for everyone in the oncology process. The PCM program could evaluate the existing education- and training programs and suggest updates for increased CEss understanding. Tthe PCM program could also offer specific training and education in relation to the implementation of CEss research.

What is needed to fulfil the suggested actions?

1. Formation of a biological-CEss research team, using the infrastructure of the clinical study/IT processes within the PCM program
2. The general project plan of the PCM program includes the actions stated here for biological-CEss research
3. Realistic timelines in the project plan with a focus on sustainability for biological-CEss research

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