Digital Home-Based Prehabilitation before Surgery dHOPE)

– PRESERVATION OF FUNCTIONAL STATUS IN PATIENTS UNDERGOING MAJOR CANCER SURGERY –

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1. Digital Home-Based Prehabilitation before Surgery (dHOPE)

– PRESERVATION OF FUNCTIONAL STATUS IN PATIENTS UNDERGOING MAJOR CANCER SURGERY –

2 INTRODUCTION

Major cancer operations are associated with a significant risk of complications and irreversible or longstanding loss of function. Patients report that they value functional capacity and independence as much as survival. Traditional *re*habilitation is hampered by being introduced at a time point when the patients' reserves are at the lowest. Data strongly suggest that an effort to increase functional reserves before the challenge of surgery – *pre*habilitation – can prevent complications and readmissions and reduce hospital length-of-stay. Most importantly, it can prevent loss of functional capacity and independency. However, a key challenge to prehabilitation is patient compliance. The available data come from hospital-based prehabilitation programs requiring patients to commute on daily basis. This has low acceptance even in densely populated metropolitan areas. By transferring of the prehabilitation to the patients' home, we will increase compliance, contribute to a future-oriented digitalization of the healthcare system, and strengthen the link between the patients and the hospital – a process that will bolster vulnerable transitions and improve patient-hospital relationship.

We will perform an RCT to scientifically test a digital home-based multimodal prehabilitation bundle to increase functional reserves in patients scheduled for major cancer surgery. We have called our study "**D**igital **Ho**me-Based **Pre**habilitation before Surgery – dHOPE". The main goal of our project is to elucidate the functional outcome of the prehabilitation program, and to assess the patient perspective through structured questionnaires of the patients' perception of their experience with the prehabilitation program (PREMs) and the effect on life-quality (HR-QoL).

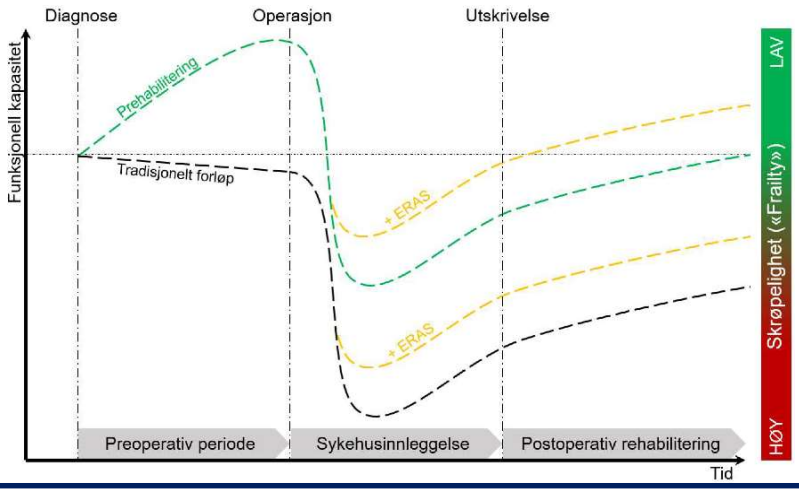

Figure 1: Illustration of the concept of how prehabilitation, in combination with ERAS, impact the patients' functional capacity before and after an operation. Prehabilitation reduce patient frailty and increase functional reserves prior to surgery. This may reduce hospital length-of-stay and the need of community based health care and support after discharge, and our pilot study suggest that the patients' experience measures and postoperative Quality-of-Life is significantly improved after the completion of a prehabilitation program (Kleve NGF-nytt 2022).

The project is multicenter and multidisciplinary and engage national- and international collaborators. We will perform an RCT to scientifically test different multimodal prehabilitation bundles to increase functional reserves in patients scheduled for major cancer surgery. The study is designed to compare a digital home-based program with a hospital-based program and no organized prehabilitation. We harvest blood samples at three time-points, and tumor specimens at the time of surgery. By combining surgical outcome, clinical data, high-throughput molecular biology and artificial intelligence we intend to identify biomarkers reliably predicting the patients' individual pre-operative risk profile and outcome after surgery. The project harbors a clear innovation potential, and the digital platform can easily be spread and implemented by all Norwegian hospitals.

Frailty is a syndrome characterized by increased vulnerability to stress, leading to increased risk of disability, morbidity and mortality. Moreover, people do not age at the same rate. Individuals with same chronological age display great differences in biological age and divergent frailty (Yang Cell 2023; Levine Aging 2018). A task of the proposed study is to establish a biobank with blood- and tumor samples for molecular analyses in search of biomarkers that reliably reflect a measurable effect of prehabilitation on the frailty syndrome and the patients' individual risk profile (López-Otín

Cell 2023). We believe some patients will benefit from a prolonged prehabilitation scheme, while others are fit for surgery after a shorter program. Biomarkers reflecting the patients' individual conditions are required to individualize the prehabilitation program according to the patients' needs. We will do genetic, epigenetic and metabolomics analyses of blood and serum, and feed results from multi-omics analyses, clinical results and patient outcome into advanced machine learning algorithms to identify possible predictors of the patients' condition and prognosis. In parallel to the data obtained from this study, our models can be pretrained on other biobanks (such as Dutch "Lifelines" or UK biobank) providing biomarkers and clinical outputs, allowing for high precision predictions and uncertainty measurements never achieved before. These analyses are done in collaboration with basic scientists at OUS (Oslo, Norway), Karolinska Institutet (Stockholm, Sweden) and PueroVita Biotechnology.

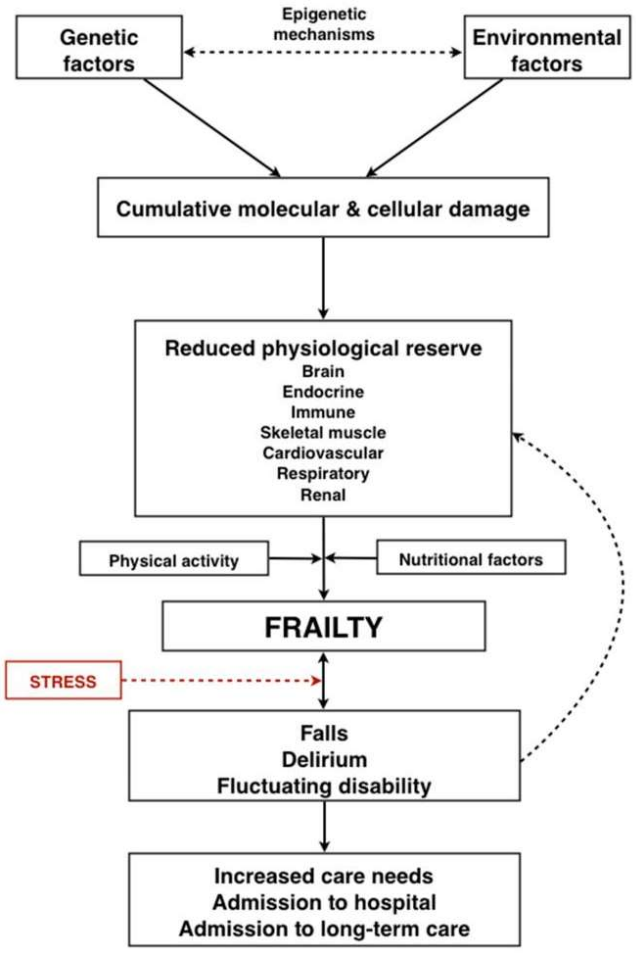

Figure 2: A schematic representation of the pathophysiology of frailty. There is a complex interplay between genetic predisposition and environmental factors that affect epigenetic and epitranscriptomic regulation in turn accelerating cellular damage and aging thus reducing functional reserves. The process can be counteracted by improved nutrition and daily exercise through a structured multimodal prehabilitation program (Clegg Lancet 2013).

2.1 EXPECTED IMPACT/BENEFIT

Functional impairment predicts post-operative complications and mortality in older adults operated for colorectal cancer (Kristjansson Crit Rev Oncol Hematol 2010; Ommundsen Europ Ger Med 2013), and numerous studies have confirmed the association between frailty and complications, slow functional recovery, and postoperative mortality, (Dale Ann Surg 2014; Wilson Br J Anaesth 2010; Gillis Anesthesiology 2014). Furthermore, the risk of a permanent reduction in functional capacity after surgery increases with pre-existing comorbidity and functional impairment (Dronkers Anaesthesia 2013). Even following the implementation of Enhanced Recovery After Surgery (ERAS) protocols for major abdominal surgery (Lassen Clin Nutr 2012; Mortensen Br J Surg 2014), and general optimization measures (Fearon Br J Surg 2013), major cancer operations are associated with a high rate of complications and constitute a severe impact on patients' levels of function (Kleve NGF-nytt 2022; figure 1). Adding to short-term complications and protracted recovery are long-term functional impairment and fatigue and reduced health-related quality-of-life (HR-QoL). Malnutrition and sarcopenia (low muscle mass) are major causes of morbidity and mortality in advanced cancer patients (Antoun Annals of Oncol 2018). Sarcopenia is associated with increased treatment toxicities as well as reduced progression-free and overall survival (Prado Cancer Chem Pharm 2011; Malietzis Br J Surg 2016). Martin et al. found that a cohort of 1473 lung and gastrointestinal cancer patients exhibiting weight loss, low muscle mass and density survived 8.4 months, compared with 28.4 months in patients who had none of these characteristics (Martin J Clin Oncol 2013). Most patients emphasize that functional outcomes after treatment, such as the ability to live independently, are more important than survival (Fried N Engl J Med 2002; Akishita J Am Med Dir Assoc 2013). Furthermore, patients who do not recover swiftly after surgery may lose the opportunity of adjuvant anti-cancer treatment. Thus, finding ways to preserve functional status is paramount.

The feasibility of multimodal prehabilitation is threatened by low compliance to hospital-based programs due to burdensome commuting even in central and metropolitan areas (Dunne Br J Surg 2016). Economical and logistical constraints in modern hospitals add to this. To build on the known benefits of hospital-based prehabilitation programs but at the same time overcome the challenge of known constraints and low acceptance to daily long-distance commuting in a vulnerable period for surgical cancer patients, a new approach to prehabilitation is warranted. Making the intervention digital, thus transfer of the prehabilitation program to the patients' own homes, is an intriguing idea (Durrand Anaesthesia 2021; Barberan-Garcia Front Oncol 2021). In addition, modern surgery is continuously pushing limits. With an aging population, surgery is offered to the very old, even centenarians, and multimorbid patients. There is an increasing need for personalized prediction of risk and outcome, not only when regarding survival of surgery and cancer, but rather with respect to level of function, activities of daily life and life quality.

3 HYPOTHESES, AIMS AND OBJECTIVES

Environmental influence, such as sedentary lifestyle, socioeconomic adversity, and malnutrition in addition to yet unknown genetic and molecular factors, underlies development of the frailty syndrome. The addition of external stress, like major cancer surgery, may be the final straw that sends the patient over the edge and necessitates increased care (figure 2).

Re-habilitation *after* surgery has been the traditional approach to counteract this unfavorable outcome but comes at a time where patients' reserves are at their lowest. Conceptually, an intervention that *predates* the trauma, i.e. applied before the physiological stress of surgery is appealing and has been coined *pre*habilitation (Carli Curr Opin Clin Nutr Metab Care 2005). A multimodal prehabilitation program includes intensive and coached physical exercise and optimized nutritional intake coupled with smoking cessation, physiological support and correction of poly-pharmacy. Indeed, such programs have repeatedly been shown to increase functional capacity (Bruns Colorectal Dis 2016; Hijazi Int J Surg 2017; Boukili Skand J Surg 2022), to reduce rate of complications in patients undergoing major abdominal surgery (Barberan-Garcia Ann Surg 2018; Heger J Gastrointest Surg 2019), to reduce unplanned readmissions (Barberan-Garcia Br J Anaesth 2019), and to lower the costs (Howard J Am Coll Surg 2019). The benefits appear even in situations where ERAS care is already established, indicating that the benefits from prehabilitation comes as an addition to what ERAS offers. The observed improvement of functional capacity appears to depend on a concomitant increase in protein intake to allow for lean muscle anabolism (Gillis Gastroenterology 2018), and studies on physical exercise alone have shown conflicting results (Lemanu World J Surg 2013; Moran Surgery 2016). Hence, an important aspect is that complementary interventions such as physical exercise *and* nutritional counselling are warranted, to help sustain or rebuild muscle mass through increasing protein metabolism and decreasing catabolism (Al-Majid Biol Res Nurs 2008).

We want to move the prehabilitation program to the patients' homes by implementing a user-friendly digital platform with daily online real-time exercise together with a dedicated physiotherapist. *To our knowledge, a digital home-based prehabilitation program is completely novel.* A home-based approach spares the patients for time-consuming and laborious commuting to the hospital, and it represents a valuable future-oriented cost-effective digitalization of the health care system. *Our long-term ambition is to spread our digital model to all hospitals nationally and implement prehabilitation for all cancer patients.*

Hypothesis: A digital home-based prehabilitation program is not inferior to a hospital-based program in preventing loss of function in frail patients undergoing cancer surgery. Advanced analytics will provide personalized prediction of surgical outcome and post-operative functional level and quality of life.

Aim: Maintain functional capacity and protect quality-of-life for patients undergoing major cancer surgery using a defined prehabilitation program and develop biomarkers reflecting patients' individual risk profile.

Objective: Stratified randomization of patients to either digital home-based or hospital-based prehabilitation, or no organized prehabilitation (control group). Evaluate change in "six-minute-walk-test" (6MWT) following prehabilitation (primary outcome). Decipher the

role of the epigenome, epitranscriptome and metabolome in relation to the surgical outcome, clinical data, and functional capacity. Utilize artificial intelligence in the multi-omics integration and pathway analyses to identify biomarkers.

Results: Development and implementation of a digital home-based prehabilitation program to improve outcome and maintain quality-of-life for patients after major cancer surgery. Novel blood biomarkers to predict outcome.

Summarized: The primary goal of our project is to develop and implement a digital home-based prehabilitation program and use this setup in an RCT to compare digital home-based prehabilitation with hospital-based or non-organized. The secondary goal is to identify blood biomarkers reflecting the effect of prehabilitation on patient frailty and reliably report the patients' individual risk profile to establish personalized prediction of outcome for patients treated for colorectal cancer.

4 PROJECT METHODOLOGY

The proposed project describes a three-armed, open-labelled parallel-group randomized controlled trial (RCT) between a control group (current practice) and two intervention groups: A digital home-based prehabilitation bundle and a hospital-based prehabilitation bundle. Patients will be extensively tested at the hospital premises at three time points to assess functional capacity. Blood samples for biomarker analyses will be drawn at the same three time-points, and tumor specimens will be collected at time of surgery. Figure 3 illustrates the trial outline. Patients are randomized to one of three possible preoperative courses, and we do a stratified randomization to include the frail, or pre-frail patients (based on "Frailty Index") to ensure inclusion of individuals with presumed effect of prehabilitation. Postoperatively, all groups enter a standard rehabilitation program to isolate the effect of prehabilitation in the analyses.

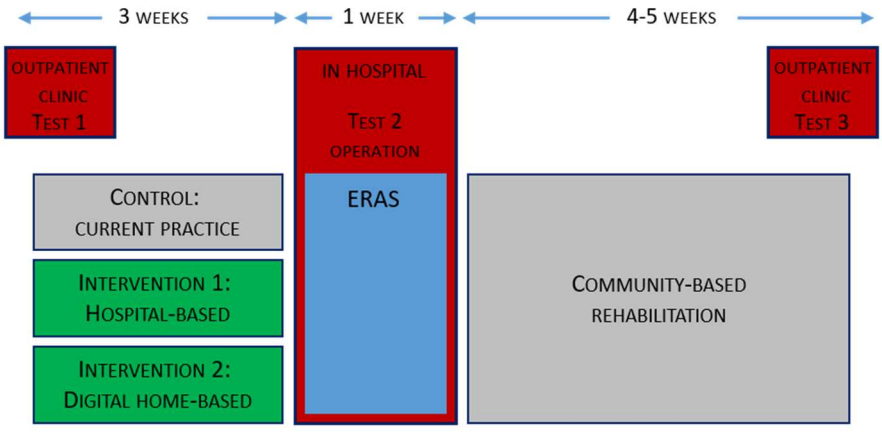

Figure 3: Overview of project timeline. Included patients will undergo a set of functional test prior to randomization to establish a baseline level to which one can compare post-prehabilitation and post-operative results. Intervention will run for three weeks before surgery, and the enrolled patients will be tested again the day before the scheduled surgery. After the operation, the patients follow standard postoperative rehabilitation, and the final test is done 4-5 weeks after hospital discharge.

Patients are screened at the preoperative outpatient clinic and invited into the trial (included) if:

- Planned for major gastrointestinal cancer surgery
- Fluent in Norwegian and able to consent and to understand questionnaires

They cannot participate (excluded) if:

- Inability to walk for six minutes or to rise independently from a chair
- Inability to comprehend exercise program or to comply with written and oral instructions
- Presence of a cardio-pulmonary condition that precludes exercise
- Living in very remote areas making a hospital-based intervention group impossible to implement
- Being without a permanent address
- Admittance to a hospital facility for > 50% of the time from diagnosis to surgery

For both hospital-based and digital home-based prehabilitation groups:

- Psychological coaching and support
- Individualized nutritionist counselling
- Coached, structured and repeated daily exercises for three weeks prior to surgery

For intervention and control groups:

- Counsel for smoking cessation
- Polypharmacy optimization
- Standard information about planned surgery, risks and precautions
- Rehabilitation in the form of once daily exercise for 4-5 weeks postoperatively

Details of the intervention groups:

- Nutritional optimization: A nutritionist will perform a structured interview, comprehensive nutrition assessment, and provide personalized dietary advice. The main goals are to avoid perioperative malnutrition and to ensure optimal protein intake to support exercise-induced anabolism, if required by nutritional support drinks. A daily protein intake of 1.2-2.0 g/kg will meet needs as outlined in surgical nutrition guidelines (Wischmeyer Anesth Analg 2018; Weimann Clin Nutr 2017; Symons J Am Diet Assoc 2009; Witard Am J Clin Nutr 2014).
- Exercise: Based on current guidelines and instructed by a dedicated physiotherapist, for 1 hour per day preoperatively to increase muscle strength, aerobic capacity and physical endurance. The digital home-based exercise will be done at home by the patients, with guidance by an online physiotherapist, while the hospital-based exercise will be done in groups at the hospital. Intensity will be based on the rate of perceived exertion using the Borg scale, a 15-graded scale ranging from very light to very hard. Resistance exercises will target upper/lower body, and abdominal muscles.
- Psychological coaching and support: Performed as one interview during inclusion, followed by weekly phone calls by a study nurse coordinator during the preoperative intervention, focusing on exercise, nutritional intake, motivation (and smoke cessation if applicable).

Estimation of sample-size (figure 4):
Patients are randomized to one of three possible preoperative courses, and we do a stratified randomization to include the frail, or pre-frail patients (based on "Frailty Index") to ensure inclusion of individuals with presumed effect of prehabilitation. Sample size calculation is based on a two-sample (repeat measure), two-sided comparison of mean changes after 4 weeks intervention compared with baseline. Based on data for the six-minute walk test (6MWT) from a pilot study, and from Montreal, on patients undergoing colorectal surgery (Li Surg Endosc 2013; Carli Br J Surg 2010), we will need 40 patients per group Expecting dropout of 15 % necessitates a total of 140 patients.

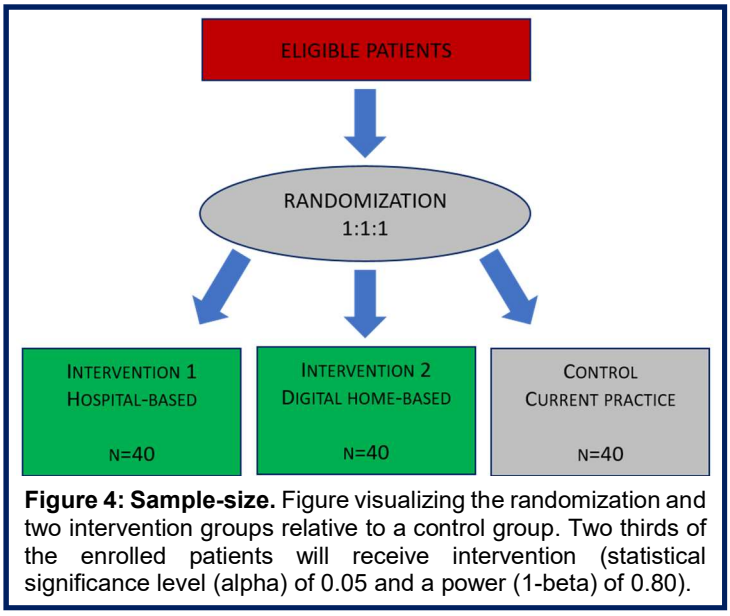

Figure 4: Sample-size. Figure visualizing the randomization and two intervention groups relative to a control group. Two thirds of the enrolled patients will receive intervention (statistical significance level (alpha) of 0.05 and a power (1-beta) of 0.80).

4.1 DESIGN, METHODS, ANALYSES

To carry out our purpose; we have defined the above-mentioned objective with connected work-packages (WP1 and WP2. See below).

Work-package 1: The primary outcome
Patients with colorectal cancer will be called and informed about the project after colonoscopy. If they decide to participate in the study, they are included at the day evaluation by the multidisciplinary team (MDT) and tested extensively. All patients get guidance by specialists in nutrition and geriatric medicine (see above). Eligible patients are then randomized, and the intervention groups receive 1-hour daily physical exercise, one group physical and one group digital. The physical group use "Pusterommet" while the digital group use the "Digitale Pusterommet". "Pusterommene" are inventions by the organization "Aktiv mot Kreft", and the project is in collaboration with them.

Change in “six-minute-walk-test” (6MWT) is chosen as our primary outcome. We will measure the walking distance at inclusion, following the prehabilitation program and 4-5 weeks after surgery. 6MWT is chosen as an indicator for functional capacity because several studies have published it to be significantly correlated with effect of prehabilitation (Boukili Skand J Surg 2022; Li Surg Endosc 2013; Carli Br J Surg 2010). Moreover, the following parameters will be addressed:

- Quality of life: Health-related-quality-of-life (HR-QoL) will be assessed by the EORTC QLQ C30, the EQ-5D and the QoR-15 tools focusing on aspects relating to functional status, emotional function, role function, pain and overall QoL
- Patient-reported experience measures (PREMs) will be measured by GS-PEQ (Sjetne BMC Health Serv Res. 2011) to elucidate the patients’ perception of their experience with the prehabilitation program and health care system
- Complications according to the Clavien-Dindo Classification
- Use of nursing home facilities 4-5 weeks post-discharge
- Changes in patient weight, energy- and protein intake
- Aggregated length-of-stay (aLoS) within 30-days from surgery and 90-day mortality
- Cost-effectiveness. This is a subtask within the field of health service research. We will estimate the resources used on the prehabilitation program and compare to resources saved by shorter aLoS, less use of nursing home facilities and less need of community healthcare services

Work-package 2: The biomarkers

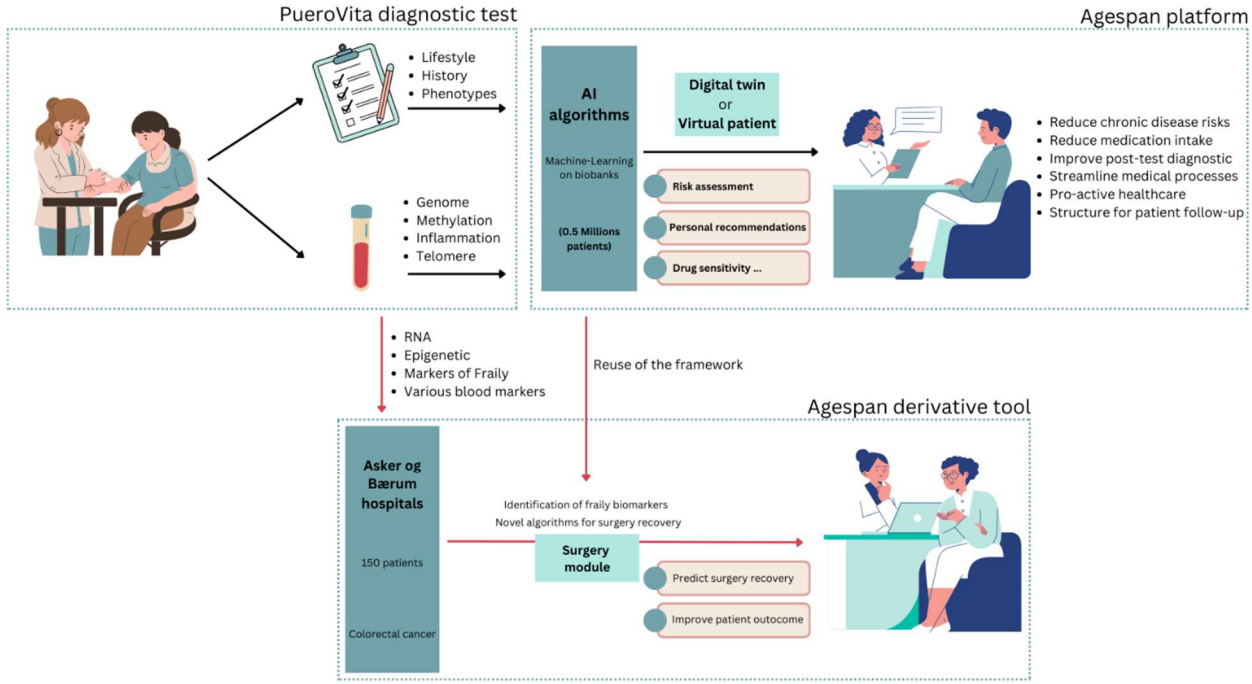

Figure 5: Workflow of AI-based analysis of multi-omics data. Epigenetics, epitranscriptomics and metabolomics are integrated and analyzed using a knowledge graph approach to stratify disease endotypes, identify relevant pathways and ultimately identify endotype-specific biomarkers with predictive value of surgical outcome.

Reversible modifications of DNA and RNA molecules, and proteomics/metabolomics, allow for rapid cellular adjustment to environmental changes, a concept well known from basic cancer research. We believe the same mechanisms plays a significant role in the patients’ adaption to the environmental change imposed by the prehabilitation program. We have recently portrayed the RNA modification status of the small non-coding RNA and elucidated their role in gene regulation (Su Nature Commun 2022). In the proposed project we will use the same workflow to portray the modification status of DNA and RNA, and include metabolomic analyses, before and after the prehabilitation program, and after the surgical stress. There are evidence suggesting that a physical prehabilitation program affect tumor growth and metastasis (Verma Immunopharmacol Immunotoxicol 2009; Amirsasan Cancer Cell Int 2022). Thus, we will compare the molecular changes in blood samples with changes in tumor cells collected at the day of the operation.

To cope with the overwhelming amount of data generated by multi-omics, we will use advanced analytics and machine learning to map the relationships between the epigenome, epitranscriptome and metabolome in relation to the surgical outcome, clinical data, and functional capacity. To do so, several unsupervised multi-omics integration and pathway analysis approaches will be tested and subsequently evaluated based on the emerging endotypes of prehabilitation samples and control samples (figure 5). By combining endotyping from the multi-omic analyses with existing knowledge graphs, we will be able to better distinguish patient endotypes and identify novel biomarkers. We will query the graph both on the basis of embedding methodologies for similarity assessment, e.g. LINE (Tang Proceedings of the 24th International Conference on World Wide Web 2015: 1067–1077), and graph neural networks. The top candidates and candidate combinations will then be tested in subsequent studies. The AI-based analysis will be done by our collaborator Dr. Valentin Normand and his team, PueroVita Biotechnology. PueroVita Biotechnology aims to improve insight into aging biology and frailty to increase understanding of aging, and what one can do to counteract frailty (https://puerovita.ai/).

4.2 PARTICIPANTS, ORGANIZATION AND COLLABORATIONS

	Name	Role
Key collaborators (curriculum vitae enclosed)	Rune Ougland Bærum Hospital	WP1/WP2: Project leader and principal supervisor
	Guro Kleve Bærum Hospital	WP1/WP2: PhD student
	Marius Myrstad Bærum Hospital	WP1: Co-supervisor
	Arne Klungland University of Oslo	WP2: Co-supervisor
	Line Schjøtt-Iversen Diakonhjemmet Hospital	WP1: Surgeon, participates in enrollment of patients and evaluation of results.
	Valentin Normand PueroVita Biotechnology	WP2: Artificial intelligence. Development of algorithms for multi-omic and clinical integration and identify biomarkers.
	Juulia Jylhävä Karolinska Institutet	WP2: Studies of aging-related frailty syndrome and epigenetics of aging including aging and frailty biomarkers.
National collaborators	Helle Aanesen Aktiv Mot Kreft	WP1: CEO of “Aktiv mot Kreft». Experience in digital physical training, and exercise as part of cancer care.
	Marianne Helgheim Bærum Hospital	WP1: Physiotherapist, in charge of the physical exercise provided to the patients in the intervention groups.
	Parasto Engene Bærum Hospital	WP1: Registered dietitian. Provides personalized dietary advice in relation to cancer and major surgery.
	Marita Tegnander Bærum Hospital	WP1: Cancer nurse, contributing in testing of the enrolled patients and has knowledge of all required methodology.
International collaborators	Cindy Neuzillet Curie Institute, St. Cloud	WP1: Experience in digital prehabilitation of gastrointestinal cancer patients from rural areas.
	Zhangli Su University of Alabama	WP2: Bioinformatics and artificial intelligence. Development of required algorithms. Multi-omics analyses.

4.3 PLAN FOR ACTIVITIES, VISIBILITY AND DISSEMINATION

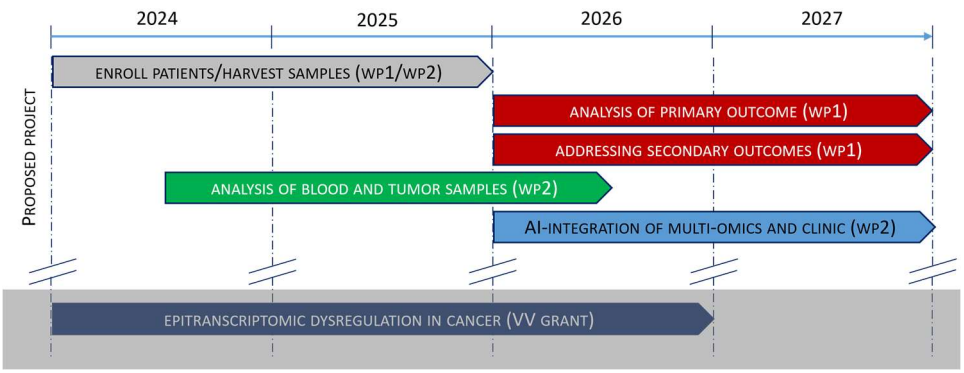

Figure 6: Overview of project timeline. The figure is a schematic suggestion and changes may apply. For statistical reasons, WP1 can first be achieved once all patients are enrolled. WP2 may start earlier than indicated. Behind the gray shading is complementary projects.

Users: The project will be carried out in collaboration with user groups and rapid dissemination of project results is expected. We will make the results of the study known to the patients and caregivers, and we will seek advice from our expert group of users to do this efficiently. Patients and caregivers may also be identified through the cancer coordinators, and we will use the network that we establish through this study to reach patients more efficiently.Community: The planning of the study will be carried out in cooperation with representatives from the municipality. As the study is multidisciplinary, we have the potential to spread the knowledge to a broad group of health professionals in the community. We will do this by arranging workshops for physiotherapists, cancer coordinators, and nurses. This educational process is an important part of the dissemination of knowledge about the effects of surgery on functional status and alertness towards preventing loss of function. After the study is completed, results will be presented at suitable conferences or other meetings. General public: Cancer is a disease with a high level of interest to the general public. The research team will reach out through social media, e.g. by blog posts, the effects of surgery on functional status, and how to prevent loss of function through exercise and nutrition. We aim to publish in national papers such as “Apollon” and “Khrono” as well as widely read scientific webpages such as www.forskning.no. We will collaborate with the Norwegian Cancer Society in order to inform the public as well as influence stakeholders such as public administration. *We are presenting the proposed project during “Arendalsuka 2022” as an initiative by “Aktiv mot Kreft”.* For the academic (and clinical) community: The primary audience of our results is scientists and clinicians working in the field, and we will publish our data in peer-reviewed scientific journals of high quality. Moreover, results will be presented at international conferences on surgery, geriatric medicine, oncology, geriatric oncology, physiotherapy, and nutrition. For clinicians in Norway, the experiences and results from the study will be presented in national journals such as “Tidsskrift for Den Norske Legeforening”, “Indremedisineren” and “Onkologisk forum”, and we aim for frequent lectures at various hospitals dealing with older cancer patients. *We have already published a description of the project (Kleve NGF-nytt 2022).*

A project progress plan with milestones is suggested (figure 6).

4.4 PLAN FOR IMPLEMENTATION

Users: In our proposed project, we include PREMs (see pt 3.1/WP2 above) to elucidate the patient perspective and develop our prehabilitation program according to the patients’ needs and desires. We scientifically test a novel intervention with a generic potential for all cancer patients that need major surgery, or even extended radiation or chemotherapy regimens. A well-functioning digital home-based prehabilitation program is a non-invasive approach that preserves functional capacity and quality-of-life, reduces complications and dovetails with the wishes of cancer patients and needs of society. Avoiding unnecessary time spent in hospital before and after major surgery and an early established digital contact with healthcare providers is in full accordance with the expressed concerns voiced by the user representatives in the team. Our focus is on gastrointestinal cancer patients as this is our clinical field, but the model will be easily applicable to other fields of cancer surgery.

Community: The project is performed in collaboration with community health care personnel: Cancer coordinating nurses and community-based physiotherapists and nutritionists, and hence has the potential to generate an increased local expertise that will outlast our project. Moreover, a digital platform for healthcare, and a community-driven home-based prehabilitation, will strengthen the interaction between "the treatment-triad" i.e. the hospital, the community, and the patients.

General public: Implementation of a digital home-based platform for physiotherapy represents a future-oriented digitalization of the healthcare system enabling the community to reach out to a large number of users in a time- and cost-effective way, in line with the goals given by the government.

For the academic community: Reversible RNA modifications allows for rapid cellular adjustment to environmental changes. This mechanism is known to play a substantial role in tumor-cell resistance against anti-cancer therapy. We believe the same family of molecules will reflect the cellular adaption to the environmental change a prehabilitation program represents. We have recently portrayed the RNA modifications of small non-coding RNA and elucidated their role in gene regulation (Su Nature Commun 2022). We will use the same workflow to portray the modifications status before and after the prehabilitation program, and after the surgical stress. *We search for biomarkers reflecting the patients' individual response to prehabilitation. This is to individualize the prehabilitation program as we believe some persons will benefit from a longer program, while a shorter one is sufficient for others. We aim to identify a panel of methylated RNAs that can serve as a useful screening tool in evaluation of operability of frail cancer patients.*

Risk assessment

In this proposal, we combine high-risk/high-gain objectives with some very feasible ones. We have recently published two manuscripts using the described sequencing methodology. Thus, the high-risk is associated with the positive outcome of WP2; namely identification of biomarkers reliably predicting the patients' individual risk profile and treatment outcome. However, with adequate resources, we believe we possess all required facilities and expertise to successfully achieve our proposed results. Some of the proposed sub-projects are very challenging (development of artificial intelligence predictive algorithms). However, the project management underscore that the challenging high-risk work tasks are already partly developed (funded by other grants), and the proposed project will get support from personnel working on these complementary projects. Moreover, PueroVita Biotechnology has particular experience in analyses of aging and frailty and will be investing considerably of their own resources into this project. Thus, although the project is laborious, we consider it completely feasible to achieve. The schematic overview of the project plan includes complementary projects on epitranscriptomic cancer research (figure 6). The proposed project will be done according to this scheme. PueroVita has extensive knowledge into translating research into product, and has built many other platform systems and software. Any discoveries worth of patenting will be brought up to the UiO/OUS Inven2 technology transfer office. Of note; the project management currently holds 8 granted and pending patents as well as 4 licensed products.

5 USER INVOLVEMENT

The patients diagnosed and treated for colorectal cancer have provided information about the life with gastrointestinal cancer, including everyday problems and quality of life. This created the desire of doing something to improve their situation. Thus, in collaboration with the organization "Aktiv mot Kreft" we initiated a prehabilitation pilot project including 20 patients who were offered daily physical exercise, psychological coaching and dietary advice. These "pilot patients" have served as our user group, and we have discussed the development of the project with them. One of the patients has served as spokesman for the group, however, because of recent severe disease progression he is no longer capable to serve the role and we have not named him in the application form. Despite this very sad development, we have maintained communication with the patient group and designed the project according to their needs. Through several meetings between patients and clinical personnel we have collected suggestions and feedback of how to best proceed with our investigations. Patients, nurses, physiotherapists, secretaries, and doctors have all contributed with invaluable input regarding the challenges coming with the disease work-up and treatment. In our proposed project, we include PREMs to monitor the patients' perspective and continuously develop our prehabilitation program according to their needs and desires. We have a dialogue with The Norwegian Cancer

Society and received results from their surveys which report that a significant number of cancer survivors want more information and supervision of how and what to do to participate in their treatment chain. When specifically interviewed about prehabilitation, more than 70% answer that they would have appreciated participation in a program such as ours.

6 ETHICAL CONSIDERATIONS

The project is approved by the Regional Ethical Committee (REC) (ref. no: 489036). Patients will be enrolled following written informed consent. Time of surgery will be postponed by 1 week for the intervention groups compared to the recommended "pakkeforløpstid". However, multiple international studies report that this delay does not improve the risk, rather the contrary; if a prehabilitation program is followed, the risk is reduced. Except for the delay of surgery, the enrolled patients follow standard diagnostic work-up and treatment common for all patients with gastrointestinal cancer. However, the enrolled patients will have to use more time on examinations and testing. The patients in the intervention groups will be followed more closely and have more focus on exercise, diet and smoke cessation. We expect all patients to benefit from the program, however, we assume that those randomized to the intervention groups will benefit more than the control group. There will be no information given to the enrolled patients about the molecular analysis. Results from the proposed project will be published in peer-reviewed international journals. It will not be possible to identify the enrolled patients in the publications. GDPR limits sharing of raw data to third party databases, and any sharing of such data will only be possible after evaluation by REC and the local Data Protection Officer. The project does not impact the environment, lead to manipulation of individuals or society, have military consequences, or expose sensitive personal information. We have a system in place to support employees who might encounter ethical objections on the work floor.

7 REFERENCES

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