The digital Experimental Cancer Medicine Team

Engaging patients, Driving decisions

2021 Report

Digital Experimental Cancer Medicine Team

CANCER RESEARCH UK | MANCHESTER INSTITUTE | CANCER BIOMARKER CENTRE

MANCHESTER 1824 The University of Manchester

NHS The Christie NHS Foundation Trust

Contents

World leading scientific research, including pioneering work in precision medicine and cancer treatment is brought together through the Manchester Cancer Research Centre (MCRC) partnership, a unique collaboration that brings together the expertise, vision and resources of its partner organisations: Cancer Research UK Manchester Institute, The University of Manchester and The Christie NHS Foundation Trust, all of which have formidable individual reputations in the field of cancer research.

Introduction

2021 was yet another challenging year for our team caused by the ongoing COVID-19 pandemic and yet, despite these challenges, which were further compounded by having to continue to work from our homes, as a team we still were able to remain extraordinarily productive, continuing to conduct novel research and innovation focused on patient-centred care pathways, ethical AI, technology clinical trials and decision science. We achieved this by remaining focused on the patient through our continued engagement with our patient communities, our colleagues at The Christie, Manchester Royal Infirmary, University Hospital Southampton and with our national and international collaborators, which include Cancer Core Europe, Target National and CRUK UpSMART Accelerator.

This report marks the first year of the implementation of our 2021-2025 digital ECMT strategy following the completion of our previous 5-year iDECIDE programme. This current programme is extremely ambitious and has required the reconfiguration of our organisational structure in to five new functional areas and leaders, who have extensive knowledge and experience in their respective fields. The new structure has been very successful and has resulted in more effective delivery of our innovation and research.

This organisational change within the digital ECMT, has already delivered dividends because of the new leadership and focus. The 'Technology' Clinical Trial team, which is now led by Dr. Donna Graham, successfully delivered Part A of the IN-HOME study, commenced the A-EYE study in collaboration with the Manchester Royal Eye Hospital, which will utilise AI/deep learning for the detection of retinal toxicities, received ethical approval for the NOTION study and successfully won funding for a project to encourage broader patient inclusivity in clinical trials from the Manchester Academic Health Science Centre (MAHSC). This project aims to reduce inequalities by bringing diverse patient groups together with research teams through a series of online workshops to create inclusivity guidance for technology clinical trials. See page 17 for a full update on the team's progress.

The Artifical Intelligence (AI) team led by Dr André Freitas, successfully delivered and implemented a dedicated AI environment for clinical AI research, which has been an important step in developing our capability in this area. The team also delivered important publications related to our CORONET.AI COVID-19 research and AI methods, which are forming the building blocks to the development of ethical AI approaches (safe, explainable and interpretable) more information on their progress can be found on page 19.

The Technology team led by Paul Fitzpatrick, has continued to innovate and develop our technology platforms to be able to conduct our technology clinical trials and deliver our open-source code to our clinical and scientific communities. These include our ACUITY Decision Support System (DSS) for analysing clinical trials in real-time, digital ECMT Cancer Trial Matching Tool and the first prototype version of Recommender Decision Support System (DSS), which is seeking to deliver optimised treatment and clinical trial options to medical oncologists and patients. Further information can be found on page 28.

One major challenge is always the management of our ever-burgeoning portfolio of research, particularly as the focus of our research work includes clinical trials, software and algorithms, which are real and tangible deliverables. The Portfolio Administration and Delivery Team, led by Laura Stephenson has ensured that our 2021 committed programme objectives have successfully delivered. A full summary of our achievements are listed on pages 27-31.

In 2021, we have welcomed new members to our team who have already integrated and strengthened our research capabilities (page 8) and strengthened our team. Their contribution has enabled us to expand our capabilities and take on larger scientific projects, while at the same time, deepen and enhance our collective knowledge and experience.

Finally, as we are an externally facing research team driven by the patient and their clinical unmet needs, our research would not be possible without their continued involvement, and we would like to thank them sincerely. Additionally, we would also like to thank our friends and colleagues at The Christie and CRUK MI, with whom we have had the good fortune to conduct and deliver successful collaborative research and technology clinical trials. We will continue this research into 2022.

Dr. Dónal Landers
Strategic Director, digital Experimental Cancer Medicine Team

digital ECMT – 2021-2025
strategic ambitions

Building further upon its 2015-2020 success, in 2021, the digital ECMT enacted its new vision to "digitally empower patients and healthcare professionals to innovate and design new cancer care pathways" and implement a new mission statement "To provide next generation patient cancer care through comprehensive data-driven evidence to enable the transformation of clinical decision-making, evolve the role of the patient, and improve patient outcomes". This strategy is being achieved by continuously listening to our patients and healthcare professionals, to understand their needs and work proactively with them in all our technology clinical trials.

In our last 2020 report we described three goals, listed below, which will deliver the digital ECMT mission and strategy. This year the team made significant progress against these goals:

1. Develop ethical algorithms (AI) to support patient care

2021 saw the establishment of a dedicated digital ECMT AI/Deep Learning research environment, which was supported by the contribution of technologies, expertise and training from AstraZeneca, Dell and NVIDIA. A number of our algorithms have been developed and tested on this platform including CORONET.AI and our reference Ethical AI architecture. AI/Deep Learning is now a core part of our technology platform and our research & innovation.

2. Build digital solutions to address clinical unmet needs

Key digital solutions delivered in 2021 included open sourcing of eTARGET, the digital ECMT Cancer Trial Matching Tool and migration from proprietary charting software for the majority of the ACUITY visualisation to an open-source alternative to enable open sourcing of the entire ACUITY codebase in January 2022. CORONET.AI version 2.0 was released to the clinical community to assist medical oncologists in assessing COVID-19 risk in cancer patients and whether their patient should be admitted or not.

3. Evaluate our technologies under clinical trial conditions (technology clinical trials).

The IN-HOME nephro-oncology trial completed Part A feasibility and opened Part B to assess clinical benefit, the A-EYE ophthalmo-oncology trial commenced recruitment, and the NOTION study received ethical approval to commence. The launch of the NOTION study is our fourth technology clinical trial.

Based upon our distinctive research capability, the digital Experimental Cancer Medicine Team (digital ECMT) continued to develop, innovate and deliver 'technology' (software, algorithms, medical devices) clinical trials, which evaluate not only performance characteristics of technology and patient / user acceptability but also clinical benefit showing how the technology enables beneficial changes in the patient care pathway inside and outside of hospitals.

Our research continues to be delivered through our five key research themes, to which we align our research programmes, projects and team resources - as shown on the right (Figure 1):

Figure 1: digital ECMT Research themes

"Many congratulations on making the eTARGET and digital ECMT Cancer Trial Matching Tool code bases open-source. It has been a pleasure to work with digital ECMT in developing these and I agree a huge success. eTARGET is always very well received by all those to whom we demo it and without doubt has filled an unmet need in clinical-genomic data integration and is integral to TARGET National/CUP-COMP. Look forward to the AI tools as part of digital ECMT's future strategic ambitions!"

Dr Matthew Krebs FRCP PhD
Clinical Senior Lecturer in Experimental Cancer Medicine, Division of Cancer Sciences, University of Manchester

The Team

For the first half of 2021, the team continued to work solely from home and meet via video conference only. Part-way into the second half of the year, we were allowed to return to the office and meet face-to-face for the first time in around 15 months. Our office accommodation also changed and moved from Alderley Park to the Oglesby Cancer Research Building in Withington. Although face-to-face office working initially felt somewhat strange, it soon became hugely beneficial to the team and collaborative working.

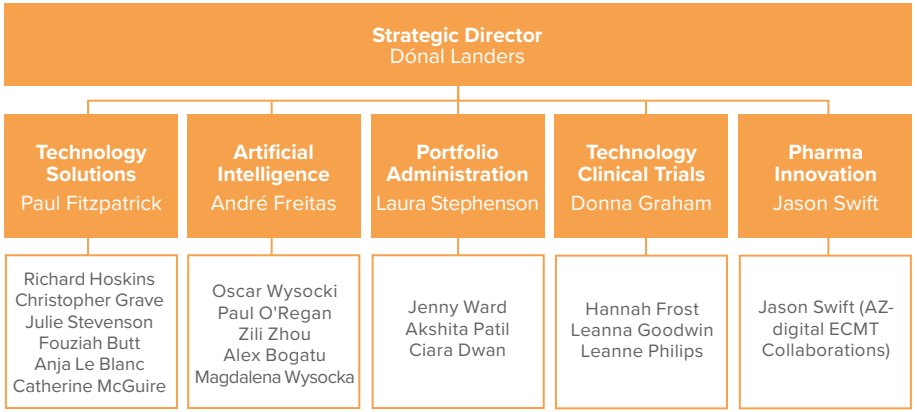
New members of digital ECMT

Our team continues to evolve to meet the demands of the projects. In 2021 we welcomed 5 new team members.

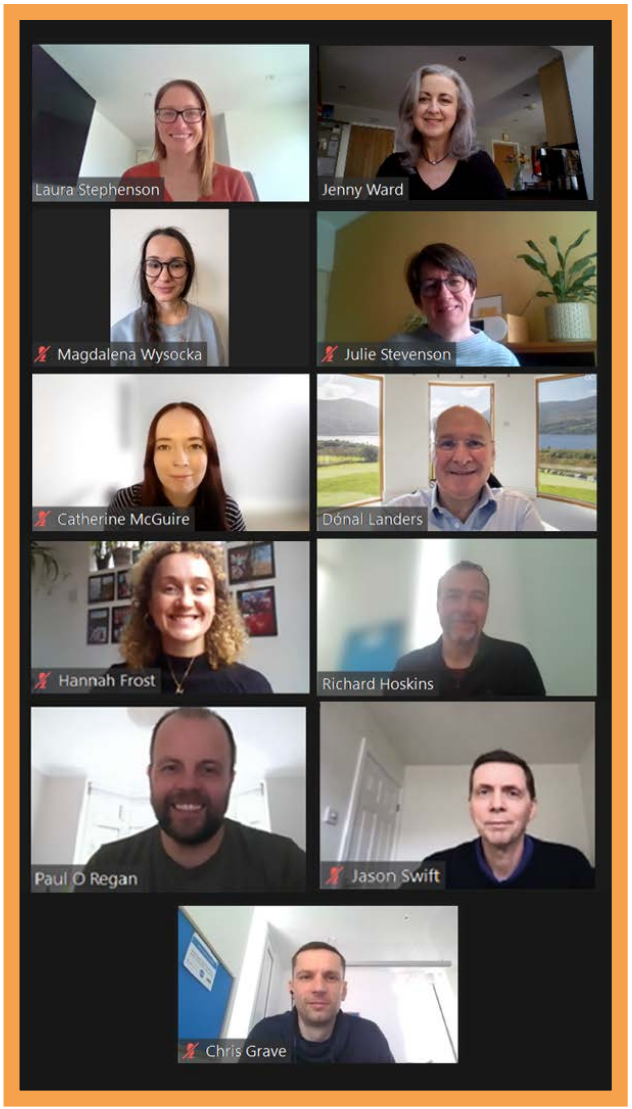
- Ciara Dwan joined us as a Research Project Manager in January and supports our research project portfolio and new grant applications. Ciara is a qualified management accountant, with experience of leading in strategy, planning, portfolio, finance and project management previously, for a variety of complex and diverse teams.
- Catherine Mcguire joined in February. Catherine has a PhD in Astronomy and Astrophysics and has worked in a variety of software development roles in both public and private sectors. More recently completing a Digital and Technology Solutions (Software Engineering Specialist) MSc at Manchester Metropolitan University, she is a Software Engineer supporting the UpSMART Accelerator programme.
- Donna Graham joined us in February as Technology Clinical Trials Lead and member of the Senior Management Team. Donna is a Medical Oncologist with the Experimental Cancer Medicine Team at The Christie and brings a wealth of knowledge of cancer clinical trials, focused on early phase research and, more recently use of technology for patient benefit – she also leads a work package within the UpSMART Accelerator consortia.
- Alex Bogatu strengthened our AI team in October joining as a Principal Clinical Informatician and is working on several AI projects, developing explainable AI systems that support clinical decision making, including CCE-DART work package 7 and iMATCH CRS algorithm development. He has a background of over 10 years in systems and software engineering, AI, databases and information technology management.
- Also in October, Magdalena Wysocka became a member of digital ECMT, as a Clinical Informatician. Her background is in biomedical engineering including working with clinical data and developing analytical methods in a clinical environment. Magdalena has a PhD in Microbial Genetics and brings knowledge of both data science of biological sciences to support our AI projects.

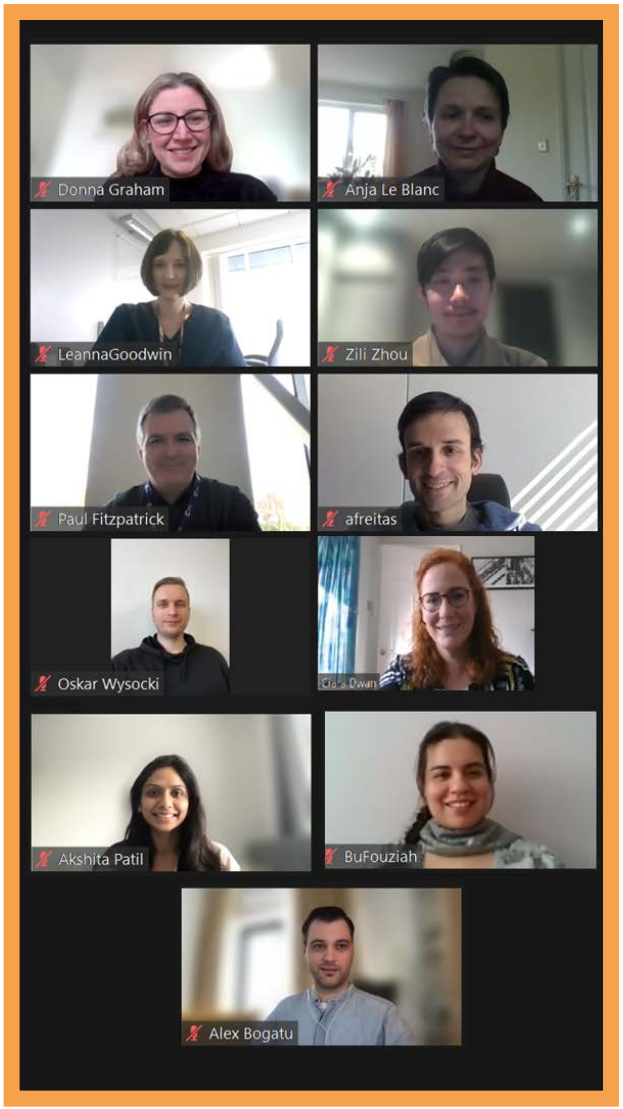
> “Since Joining digital ECMT in Jan 2021, I have had the opportunity, as research project manager, to get involved in a wide spectrum of the teams research and to support some truly innovative projects including, Treatment selection decision support tool for Breast Cancer with AstraZeneca; developing a clinical trial to determine the use of digital tools in assessing patient reported outcome measures as part of CCE-DART and developing an algorithm to predict CRS as part of the iMatch program.
>
> 
>
> digital ECMT is a highly motivated, focused, multidisciplinary team and I have thoroughly enjoyed being part of it and working with our collaborators to deliver our novel research. I look forward to all we can achieve in 2022.”
>
> **Ciara Dwan**
> *digital ECMT Project Manager*

digital ECMT organisational structure 2022



Meet the Team





2021 Timeline

2021 was another busy year for the digital ECMT, in terms of bedding down our new organisational structure, Implementing our 2021-2025 strategy, while still maintaining our momentum and continuing to deliver solid research and innovation. Some highlights of our work over the year are shown below.

January

COVID-19 lockdown again and working from home continues.

February

Cancer Trial Matching Tool made available as a stand-alone web tool to match patients to the right clinical trial.

Successful Part A (feasibility study) of IN-HOME Clinical Trial allows Part B to be set-up (see p14).

CCE-DART successfully launched (see p25).

April

iMATCH programme extended with additional funding to further develop cytokine storm release algorithm and cytokine laboratory assays under "RUNWAY" title.

CRUK UpSMART Accelerator Award held its first multi-national Scientific Advisory Board Meeting.

May

Version 2.0 of COVID-19 Risk in ONcology Evaluation Tool (CORONET) released (see p35 for web link).

June

The University of Manchester sponsored A-EYE Clinical Trial, opened to recruitment at Manchester Royal Eye Hospital (see p15).

July

eTARGET tool, integrating patient's genomic profile with their clinical characteristics, made available.

In collaboration with AZ, Recommender project initiated to develop treatment decision support tool for Breast Cancer clinicians.

eTARGET tool to be deployed to The Christie sponsored CUP-COMP and TARGET National studies.

2021

August

Dr. Donna Graham wins Manchester Academic Health Science Centre (MAHSC) Cancer Domain Funding for the "Encouraging Inclusivity in Technology Clinical Trials" project.

Code base for Cancer Trial Matching Tool made open source enabling sites outside of UK to host own version of the tool.

September

Majority of the digital ECMT met at Oglesby Cancer Research Building (OCRB) for first time since March 2020!

Circulating tumour DNA guided Adaptive BRAF, and MEK Inhibitor therapy (DyNAMIc) study awarded to The Christie and includes use of digital EMCT's ACUITY visualisation tool.

October

IN-HOME Clinical Trial Part B recruits its first patient (See p14).

digital ECMT maintains cyber essentials accreditation.

December

NOTION Clinical Trial given Sponsor Green Light approval by The Christie to start recruitment.

Recognition of CORONET team as "trailblazers in COVID-19 Research Response" at National Institute for Health and Care Research (NIHR) Clinical Research Network (CRN), Greater Manchester's Evening of Excellence.

GM Cancer Podcast: Leanna Goodwin spoke about her motivation to work as a Research Practitioner for digital ECMT and Experimental Cancer Medicine Centre (ECMC) Manchester.

The Technology Clinical Trial

Delivering tomorrow's clinical trials today

2021 was a challenging but rewarding year for the Technology Clinical Trials group. The impact of COVID caused delays to all aspects of our Technology Clinical Trials, but through perseverance we managed to commence our third Technology Clinical Trial. One important component of our research is the patient and how we ensure, and encourage, involvement of underserved communities. This is particularly relevant to Manchester, a city with a diverse population and a high level of social deprivation. Lack of diversity in clinical research is an increasingly recognised issue and increased reliance on technology during the COVID-19 pandemic has highlighted a digital divide which is a relevant risk for our studies. Technology can be utilised to bridge these gaps if used in a manner that is accessible to underserved communities. Our goal is to avoid exclusion of any community by using technology in a way that facilitates democratisation of healthcare to bring cancer care closer to the patient's home.

Despite the continued challenges faced by COVID, we continue to make good progress. We now have three studies open and actively recruiting.

IN-HOME

Phase 1 clinical studies often have eligibility criteria that prevent patients with reduced renal function from accessing the trial drug. Often these criteria are not reflective of the mechanism of the drug, or the toxicity profiles and these drugs remain untested in these populations until they are in mainstream circulation. Improved monitoring of renal function could potentially lead to earlier detection of adverse renal events and improve patient outcomes, alleviating the risk of patients with reduced renal function going on to clinical trials.

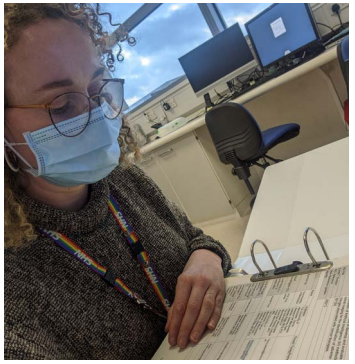
The IN-HOME study assesses the feasibility and acceptability of using a whole blood creatinine POCT device (NOVA Biomedical StatSensor® Xpress) to monitor patients kidney function whilst receiving potentially nephrotoxic anti-cancer treatments. digital ECMT have been working on this project for 4 years now, developing and implementing the end to end process by which creatinine can be monitored by patient in the home and an AKI assessment made and reported to an appropriate clinician. Part A of the trial opened in late in 2019, but due to COVID-19 had delays to recruitment when research trials were paused. In Q1 of 2021, we managed to complete Part A of the study having enrolled 13 Head and Neck cancer patients and 1 ECMT Breast cancer patient.

Based on the successful results from the Part A feasibility assessment, which showed that intensive home monitoring of creatinine with a POCT device is acceptable for patients receiving cancer treatments, with a high degree of patient compliance, Part B of the trial has now opened to recruitment. This part of the trial aims to assess the clinical benefit of home based creatinine monitoring by evaluating the potential for earlier diagnosis of AKI / change in renal function in cancer patients with intensive home monitoring.

A-EYE

This ophthalmo-oncology project was initiated to try and address resourcing issues which can leave cancer patients, particularly those on early phase cancer clinical trials, without specialist eye treatment and support. Novel cancer therapies often have unknown toxicity profiles that can include changes to the eye. Often ophthalmology expertise is lacking and only engaged after patient's eye toxicities have become advanced, furthermore, lack of expertise often means that waiting times for patients are significantly delayed.

The University of Manchester sponsored A-EYE study, aims to develop new AI methods to detect adverse retinal abnormalities associated with cancer treatment and assess against ophthalmologists' decisions. This study opened to recruitment at the Manchester Royal Eye Hospital in June 2021 (our collaborators on this study). By the end of 2021, we had approximately 220 out of 350 patients recruited to the study. The data collected from the patients includes their anonymised eye scan alongside relevant clinical data. Our AI team are using these to develop and test an ethical and explainable algorithm to detect eye toxicities from eye scans.



Above left, Hannah Frost, digital ECMT Clinical Trial Coordinator, on-site at MRI working on the A-EYE study

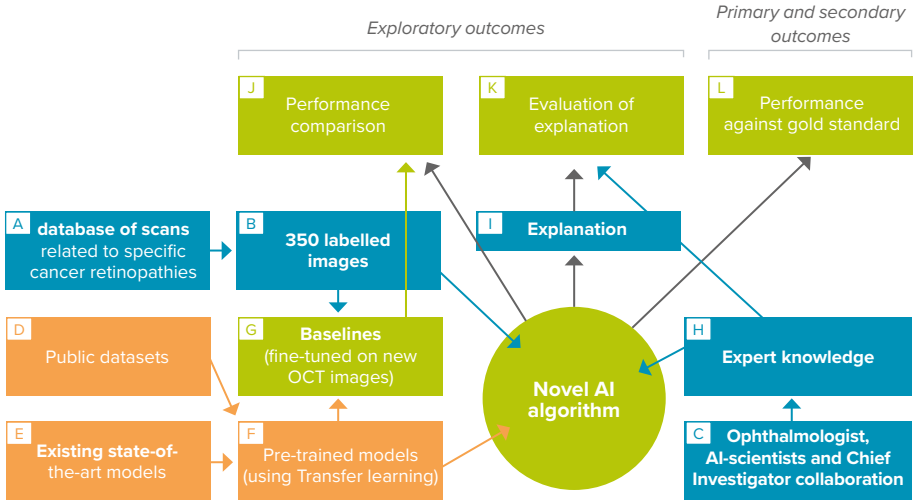


Figure 2: AI algorithm development diagram

NOTION

Immune related adverse events are side effects from cancer immunotherapies. These adverse events are very common with up to 90% of patients experiencing side effects on combination immunotherapies. Early evidence suggests that changes in cytokines correlate with the development of immune related adverse events. Therefore, monitoring of cytokines may help detect the onset of side effects and help manage them better for patients. The NOTION study (iN-hOme sampling of cyTokines in Immunotherapy patieNts) is a feasibility study to assess whether patients will take blood samples at home. The blood samples will be analysed retrospectively to assess whether changes in patients' cytokines correlate to the development of immune-related adverse events. The NOTION study is a great example of collaborative working. We have partnered with the Immuno-Oncology group at The Christie to develop the study protocol and research package. Additionally, we have worked closely with the CRUK MI CBC Cells and Protein Team, Tumour Immunology & Inflammation Monitoring Lab to validate the lab method for detection of cytokines from a dry-blood spot sample.

We were delighted when the NOTION study received ethical approval and sponsor green light in 2021 and has now opened to recruitment as of 27/01/2022. Recruitment will be extended to February 2023 due to the delays in set up caused by COVID-19. Up to 30 participants will be recruited from Renal, Melanoma and Lung clinics at The Christie.

Images provided by Neoteryx, LLC

Successful MAHSC Cancer Domain Funding for short project - "Encouraging Inclusivity in Technology Clinical Trials"

Clinical trials exist to determine safety and efficacy of emerging therapies or interventions; participants should therefore be representative of all patients. Despite a global increase in trial participation, trial population diversity remains an issue, within the UK and globally. Our technology clinical trials are designed to use digital technology (e.g., devices or mobile applications) to develop new technologically enabled healthcare pathways through empowerment of patients to become co-researchers. It is hoped this will ultimately increase accessibility of healthcare for patients, with reduced intensity of hospital attendance. However, it is acknowledged that using technology may inadvertently exclude certain groups.

However, there is a growing appreciation of the impact of a "digital divide" in healthcare technology which should be addressed during study design to ensure modified care pathways are inclusive to all. In 2021, we were successful in a Manchester Academic Health Science Centre funding proposal, and in August initiated a 7-month collaboration with specialist organisations including Vocal (a Manchester-based not-for-profit organisation which brings people and health research together) to create agreed inclusivity guidance for future

development of technology clinical trials across Greater Manchester and beyond. We hope to ensure that our future healthcare pathway development is designed to include all patients, regardless of access and skill with technology.

Vocal and digital ECMT facilitated 3 half-day online workshops over a 6-month period. These involved patients and their representatives from diverse backgrounds, healthcare workers and researchers with an interest in digital healthcare and inclusion. The aim of the workshops was to create inclusivity guidance for development of Technology Clinical Trials across the Greater Manchester Region, ensuring that future healthcare pathway development is designed for all. During the workshops, the processes of developing, establishing and running a Technology Clinical Trial were discussed and evaluated.

This process helped digital ECMT to reflect on our Technology Clinical Trial design from different perspectives, and conducting workshops highlighted immediate changes that we could make in addition to changes to trial management processes and communication that we will be building into our trial processes. More broadly it highlighted the value of collaborating with others to both question practice and identify solutions. The legacy of this project will be to make our processes and practice more inclusive in all future Technology Clinical Trials, and to contribute to the wider discussion of addressing the digital divide in

> “Despite the continuing challenges of the pandemic, 2021 was a really fulfilling year for me as a Research Practitioner working on our Technology Clinical Trials. A personal highlight for me was the successful completion of Part A of our IN-HOME trial, and the evidence that this has given us to continue with the research, which will hopefully be able to provide clinical benefit for our participants”
>
> 
>
> **Leanna Goodwin**
> *digital ECMT Research Practitioner*

Decision Science

Supporting the way we interpret clinical trials and make decisions

The Artificial Intelligence group has seen the formal establishment of an AI/Deep Learning research and innovation capability within the group. A core part of our remit is to develop safe and ethically designed algorithms that augment clinical decision making. The team’s research focus is on the application and adaptation of new analytical methods to support better inference and clinical decision making in oncology. Our goal is to ensure that our algorithms adhere to the core medical ethical principles, so that they are safe, explainable, interpretable and are developed using non-biased datasets, which are representative of all patients.

Our research in 2021 has demonstrated that emerging AI-based analytical methods can address current paradigmatic challenges in cancer research such as enabling biomedical ‘reasoning’ over small patient cohorts, integrating available pre-clinical and clinical data/evidence, and improving the understanding of complex biological mechanisms.

The group’s AI research integrates three strategic perspectives:

1. Development of AI models which can integrate prior biomedical knowledge to support data-efficient inference.
2. Development of safe, explainable and ethical AI models suitable for clinical applications.
3. Pragmatic integration and critical evaluation of AI models in the clinic.

Application areas include the development of new AI-based biomarkers, better treatment recommendation and prediction of toxicities and adverse events.

AI Research Projects

In 2021, the digital ECMT advanced the following research Projects.

CORONET – Clinical decision support for cancer patients with COVID 19

In partnership with Dr. Rebecca Lee, Clinical Lecturer, Medical Oncology, UoM and Dr. Anne Armstrong, Consultant Medical Oncologist at The Christie and University of Manchester colleagues, we developed CORONET (COVID-19 Risk in Oncology Evaluation Tool) to support clinical decisions for cancer patients with COVID-19. Over the course of the pandemic, we built and systematically updated one of the largest datasets containing patients with cancer and COVID-19. To achieve this, we developed a data collection protocol (using REDcap, a Research Data Collection Service) allowing for standardised data upload. Anonymised data was contributed from 12 participating hospitals in the UK, 2 hospitals in Spain, 4 hospitals in the USA, and the European Society for Medical Oncology (ESMO) CoCARE registry (COVID-19 and cancer, cohort study).

Simultaneously, we developed the online tool to support decisions regarding hospital admissions or discharge in cancer patients presenting with symptoms of COVID-19 and the likely severity of illness.

University Hospital Southampton collaboration

Supporting clinical decision making during the COVID-19 outbreak (in collaboration with The University Hospital Southampton - UHS). We have continued our collaboration with UHS for the analysis of patient-level COVID data across different disease variants. Our analyses have evolved over the course of the pandemic in line with emerging understanding of COVID, and to reflect key clinical questions. As subsequent waves of infection and different viral strains emerged in the UK, we initially focussed on the characterisation of differences in biochemistry, treatments and outcomes. More recently, analysis of longitudinal data through dynamic time warping enabled us to identify those assessments with greatest clinical utility in assessing patients' clinical courses. These findings led to publications in the Journal of Clinical Virology and the British Medical Journal. As COVID moves towards endemicity in the UK, the current focus of the team is to evaluate the burden of hospitalisation.

Safe, Explainable & Ethical AI in Cancer

Developing AI models suitable for Healthcare (Safe, Explainable & Ethical AI in Cancer). We performed a systematic investigation on the suitability of explainability mechanisms within AI models via direct engagement with healthcare professionals. The effort included a systematic critical user study on the explainability properties among healthcare professionals, aiming to assess the communication gap between explainable AI models and healthcare professionals.

> "As a clinical informatician working on digital ECMT research projects, it has been fascinating to talk to Clinicians to get their views about AI-based decision-making in healthcare applications. It has indicated a clear need to introduce transparency of interpretable methods which can build trust and credibility. This will hopefully facilitate adoption of the AI tools by healthcare professionals."

Magdalena Wysocka
digital ECMT Clinical Informatician

Cancer Trial Matching Tool

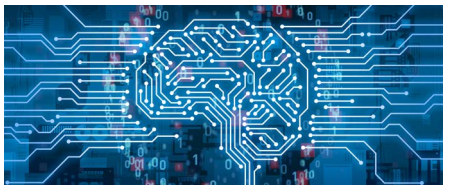
Clinical decision support for Cancer Clinical Trials. The Cancer Trial Matching tool, previously developed in collaboration with clinicians at The Christie, is an application that supports clinicians in identifying precision medicine clinical trials for patients based on their tumour genotype. Through 2021, we continued our research into the development of frameworks to support cancer treatment decisions on the basis of molecular biomarkers. This tool has been integrated into molecular tumour boards for the TARGET NATIONAL and CUP-COMP trials, which together aim to identify matched clinical trials for over 5,000 patients. The tool has been made available through an open-source licence via the UpSMART programme (page 22)- our partners at Vall d' Hebron Institute of Oncology (VHIO) have downloaded and deployed a second instance of the software for use by clinicians in Spain, and we are in discussions with potential new collaborators in France.

Recommender Decision Support System

Clinical decision support for advanced breast cancer patients. In July 2021, we initiated a collaboration with AstraZeneca (see page 27) to develop a prototype recommender system to support treatment decisions for advanced breast cancer. This included the extraction of relevant survival data at scale, evaluation of the relevance for the patient in question, and a bespoke user interface to allow clinicians to explore recommendations. The model was co-designed with Oncologists.

iMATCH

Building analytical models which integrate and use maximum evidence (predicting toxicity and adverse events). In collaboration with clinicians and scientists at both The Christie and CRUK MI Cancer Biomarker Centre, we have developed a decision support model that helps clinicians in identifying patients developing cytokine storm scenarios and making appropriate adaptive decisions to ensure safe delivery of ATMPs. The proposed model systematically integrates evidence available from previous clinical studies (regarding cytokine levels in CRS versus non-CRS patients). This has been used to develop an explainable & evidence-based model, which has then been tested against real-world clinical data.



UpSMART Accelerator update

The digital ECMT, along with our EU colleagues, including those from Fondazione IRCCS Istituto Nazionale dei Tumori Milano and Instituto de investigación Oncologica de Vall d'Hebron, Barcelona continued to work collaboratively on the 5-year CRUK Accelerator Award, UpSMART, to enable SMART Experimental Cancer Medicine Trials. Year 2 of the UpSMART award (2021) has been another busy year. As part of the strategic plan, several Digital Healthcare Products (DHPs) were identified, aligned to either work package 1 (data acquisition) or work package 2 (data interpretation) and prioritised for development and making available to the UpSMART network of 24 sites during 2021. By the end of Year 2, UpSMART has 6 Digital Healthcare Products (DHPs) that have been made available, either by open source / free to use licence or open access web-based URL, to the network of 24 sites. These are the digital ECMT Cancer Trial Matching Tool, Cancer Trial Finder Template (The Christie Lung Team), eTARGET (digital ECMT), CORONET (The Christie / digital ECMT / UoM), Phase 1 Prognostic Online tool (Vall d'Hebron), ACUITY* free-to-use (digital ECMT). An additional 5 DHPs have been prioritised for development in Year 3.

Opportunities for a multinational multi-centre technology clinical trial using Spanish funds and accelerometer devices provided by the NIHR Biomedical Research Centre at Leicester have been discussed and scoped out by digital ECMT, Manchester ECMC, Leicester ECMT and Vall d'Hebron Institute of Oncology, with a research package for conducting the technology clinical trial in development.

As part of work package 3, a training network has been established to support the development, review, and use of training materials. The primary aim of the training materials is for them to be used to upskill the phase 1 community to enable sites to set-up and deliver their own technology clinical trials to assess the feasibility and clinical benefit of DHPs.

Work package 4 continually supports the development, release and uptake of DHPs ensuring they align against the framework with regards to maturity and purpose and DHPs made publicly available have an appropriate licence and infrastructure in place. An important example of this has been the successful re-development of ACUITY* during Year 2 to remove a proprietary dependency. This was a significant piece of work that will enable us to release a fully open-source version of the visualisation tool for implementation and deployment in Year 3. Another key activity for 2021 has been the re-development of PROACT by the Milan team. WP4 has transferred knowledge on the system and Milan have successfully put in place a project manager and software engineers to redevelop the PROACT tool – used for improving the communication between patients and their healthcare team whilst on a clinical trial.

In 2021, an international multidisciplinary Scientific Advisory Board (SAB) was established with 5 members, comprising of both data science and translational research experts. The first UpSMART SAB (April 2021) provided an independent review of the programme and endorsed its outputs and future direction. The SAB will continue to meet annually, ensuring that the UpSMART programme is considering the current digital healthcare research landscape and the unmet needs in early phase cancer research.

As an easy, one-stop-shop for information relating to UpSMART and its DHPs, the UpSMART website **(https://upsmart.digitalecmt.com)** has been launched and continues to be evolved to meet the needs of the network. The list of commercial products and workbooks used by centres during various stages of clinical studies, compiled during 2020, has also been made available to the network via the website.

> "Early phase trials are challenging as there is the need to analyse large volumes of data in real time as dose decisions are made. Through work package 2 we are exploring the utility of digital technology to improve this process. The release of a free to use version of ACUITY*, a DHP to allow visualisation of trial data has been a significant milestone for the accelerator to meet this aim."

Dr Louise Carter
Senior Clinical Lecturer in Experimental Cancer Medicine. Honorary Consultant in Medical Oncology

*ACUITY is the name of the tool previously known as REACT.

digital ECMT – 2021 report – UpSMART Accelerator Award

Cancer Core Europe building DAta Rich clinical Trials (CCE-DART)

> “2021 has been a very intense and hard-working year for the Italian team regarding the development and improvement of the mobile App PROACT. This tool will be innovative in the clinical studies and with a significant social impact in the communication between cancer patients and medical teams.”

Laura Russo, BSc, MSc, Project Manager
Fondazione IRCCS Istituto Nazionale dei Tumori, Milan

UpSMART Accelerator Work Packages

1	2	3	4
DHPs for Data acquisition	DHPs for Data interpretation	Training on setup and conduct of Clinical Trials for DHPs	Technical Hub for deployment & adoption of DHPs

Figure 3: UpSMART Accelerator Work Packages

DHP = Digital Healthcare Product

Building on the partnership that was embedded in 2020 with our Spanish and Italian colleagues on the UpSMART programme, digital ECMT were invited to join a consortium in a bid to secure EU funding from Horizon 2020. The application for CCE-DART was led by Vall d’Hebron and partner sites across Europe. At the end of 2020, it was confirmed that the application was successful, and the programme was initiated in Q1 2021. The programme is for 3 years and consists of 18 work packages (WP) of which the digital ECMT will lead on two, firstly, WP7 on the discovery of multi-layer complex biomarkers and secondly, WP12 on the development of online tools for Patient Reported outcome (PRO) measurements (in conjunction with the National Cancer Institute – NKI Amsterdam).

Discovery of multi-layer complex biomarkers

In collaboration with the Karolinska Institute, we are developing new deep learning methods to support the development of new multi-omics biomarkers in the context of Breast Cancer. The AI team are systematically and critically assessing the impact of emerging Deep Learning models to support the development of new complex biomarkers. So far, we have highlighted the gaps between Explainable AI (XAI) and biological interpretability and focused on the contribution of AI for the biological understanding of oncogenic processes, in particular, the methods for integrating existing expert domain knowledge (DK) into such models. Clear trends can be identified, such as the integration of prior biological knowledge (e.g., pathways or Protein-Protein-Interaction networks).

Development of online tools for Patient Reported outcome (PRO) measurement

As a partner in the CCE-DART consortium, we are collaborating with Dr Frans Opdam at the NKI to deliver a feasibility sub-study designed to investigate the experience of patients and health care workers in the use of digital tools to collect clinical data on patients’ well-being and adverse events. This will be a multisite Technology Clinical Trial delivering Patient Reported Outcome Measures (PROMs) and toxicity data from the ongoing CCE Basket of Baskets (CCE_BoB) trial using online tools at 5 centers in the CCE consortium. We will implement two digital systems (PROACT 2 and PRO-CTCAE) in BoB as a technology clinical trial arm to capture Patient Reported Outcomes

(PRO) and drug toxicities. This study will look to evaluate the feasibility of using applications to report the effects of drugs in patients on the basket of basket (BOB) trial and to better understand both the toxicities experienced by patients administered new drugs, as well as the impact of these on their quality of life. The trial is expected to begin in the second half of this year with a read out in late 2024.

> "With DART we are aiming to improve patient care by implementing tools in clinical trials in a European collaboration."

Dr. F.L. Opdam, MD, PharmD, PhD
Medical oncologist-clinical pharmacologist. Netherlands Cancer Institute, Amsterdam, the Netherlands

Cancer Core Europe building DAta Rich clinical Trials

Digital Experimental Cancer Medicine Team

Cancer Core Europe

DART

Collaborations and Grants / Awards in 2021

AstraZeneca

The TWINKLE study

AstraZeneca, in collaboration with the digital ECMT, investigated the use of the PROACT (Patient Reported Opinions About Clinical Tolerability) mobile app for the assessment of novel digital biomarkers as part of the TWINKLE study (NCT04200326).

Briefly, the aim of this study was to explore the use of novel technologies in a real world setting to detect early changes in quality of life (QoL) following treatment for severe uncontrolled asthma. Information about asthmatic patients' disease control and quality-of-life (QoL) was measured daily using traditional patient-reported outcomes (PROs), together with electronic questionnaires, home-based spirometry (lung function breathing test) and daily video recordings using the PROACT app. Patients' QoL was assessed based on both sentiment analysis of the PROACT message transcripts and facial emotion detection of the PROACT videos.

Five patients were recruited before closing early due to COVID-19. Each patient recorded daily measurements using 3 categories of devices (electronic questionnaire, spirometry, video messaging) over a period of 6 weeks (2 weeks prior to and 4 weeks after starting treatment).

From the PROACT daily video recording transcripts, sentiment scores based on natural language processing captured significant QoL changes. However, emotion detection based on video was more variable as "baseline" emotions differed between patients. Nevertheless, video analysis showed utility in detecting QoL changes with appropriate personalized calibration.

This study showed that personalisation of emotion detection based on voice recordings, and structured interviews are interesting areas to explore further. Integrating digital therapeutics in asthma drug development trials may prove to be feasible and valuable, since the connected digital devices and artificial intelligence for sentiment/emotion analysis could capture subtle QoL changes reliably and earlier than PROs, potentially reducing burden and improving disease management.

The full paper, published in 2021, is available to members and Institutions with access to the Institute of Electrical and Electronics Engineers (iEEE) Xplore via the following link:

https://ieeexplore.ieee.org/document/9629985

> “AstraZeneca were delighted to collaborate with digital ECMT and Guy's and St Thomas' hospital on the Twinkle study, which demonstrated the capability to collect richer information about patients' experience following use of medicines in a real-world setting, and to measure novel endpoints using advanced artificial intelligence methods.”

Jason Swift
Senior Director, Precision Medicine and Biosamples, R&D Oncology, AstraZeneca. Pharma-Innovation, digital Experimental Cancer Medicine Team

Recommender Decision Support System

With the current emergence of complex multi 'omic' biomarkers and an ever-broadening range of breast cancer treatment options, it is becoming increasingly challenging for the treating oncologist to be able to synthesise the vast amount of published scientific and cancer treatment data to determine the best treatment option for a patient at a given time. The clinician must consider the molecular and microenvironmental profile of the cancer, the patient's clinical phenotype, prior treatment and available therapy options and then present, explain and discuss these treatment options to the patient in a very busy Outpatient Department (OPD) setting.
The 'Recommender' Decision Support System (DSS) collaboration with AstraZeneca was established to address this clinical need and growing decision complexity by providing the medical oncologist and cancer patient with treatment options utilising AI, clinical data, Real World Data and integrating these DSS to support the evolution of the care pathway in the clinic. A prototype version of the DSS, using metastatic breast cancer data, was successfully presented to AZ in December.

> “Working with the cross-functional digital ECMT team including Clinicians, Machine learning experts and Software engineers enabled us to build a prototype of a diagnostic recommender system for breast cancer patients. We are very much looking forward to continuing this cutting-edge collaboration to develop tools helping clinicians and breast cancer patients navigating their disease journey and offering best possible diagnosis and treatment options. Thanks for great collaboration.”

Joachim Reischl
VP, Head of Diagnostic Sciences, AstraZeneca

DELL/NVIDIA/AstraZeneca

In 2021 we received a donation of high-performance servers plus Graphics Processing Units (GPUs) with AI technology implementation expertise from all three organisations to support the research of our newly instantiated digital ECMT AI/Deep Learning team. This capability has enabled the team to embark on exploratory research into ethical clinical AI algorithm development with a vison of improving patient outcomes through proven use of ethical and explainable AI algorithms to improve clinical decision making in oncology. This environment is already delivering an impact on our AI research in a number of our collaborations including CCE-DART and iMATCH (early detection of Cytokine Release Syndrome caused by immunotherapy agents).

iMATCH (Innovate Manchester Advanced Therapy Centre Hub) and RUNWAY

Due to the pandemic, 2021 saw an extension to the 5-year iMATCH programme and in April 2021, the 1-year RUNWAY extension began. The objective for the digital ECMT remained the production of an ethical and safe algorithm that would predict the onset of Cytokine Release Syndrome (CRS) in Advanced Therapy Medicinal Product (ATMP) Patients. Small data sets and challenges with accessing them, limited the application of standard machine learning techniques. Consequently,

our AI group explored more innovative deep learning methods to enable the development of the algorithm (including the use of publicly available Covid 19 patient data; Knowledge Graphs - Clinician Interviews; Literature reviews – NLP). Also in 2021, the NOTION study was initiated which will enable the delivery of data sets more broadly related to the collection of immune toxicities secondary to immunotherapy treatment to build the research capability. The project is in a good position to deliver on its objective by the closure of iMATCH and RUNWAY on 31st March 2022.

> “I’m delighted that AstraZeneca along with DELL, NVIDIA are supporting charitable research, academic and clinical institutes across the UK digitally empowering patients and healthcare professionals to innovate and design new cancer care pathways.”

Dr Amrik Mahal
Global Head of IT for Research, AstraZeneca

The Christie NHS Foundation Trust

In addition to the NOTION and IN-HOME clinical trials, digital ECMT have continued their collaborative work with The Christie on various projects in 2021.

The code base for the eTARGET decision-support system, which integrates the patient’s genomic profile with their clinical characteristics, and the digital ECMT Cancer Trial Matching Tool, which helps clinicians identify the right clinical trials for patients based upon their cancer type, genetic alterations and/or trial drug mechanism, were made open source in July and August respectively, by the UpSMART programme. Since then, digital ECMT have hosted and supported an instance of these tools which are being actively used at the Molecular Tumour Board (MTB) meetings for two multi-site clinical trials led by Manchester ECMC and sponsored by The Christie - TARGET National and CUP-COMP.

Professor Paul Lorigan and Dr Rebecca Lee at The Christie were successful in their bids to Pierre Fabre and The Jon Moulton Charity Trust (a registered charitable organisation) to run a non-commercial investigator led clinical trial investigating Circulating tumour DNA guided Adaptive BRAF and MEK Inhibitor therapy (DyNAMiC) for the treatment of stage III un-resectable or stage IV BRAF mutant metastatic melanoma. The study includes the use of digital EMCT’s ACUITY visualisation tool to enable real time ctDNA monitoring alongside the clinical data to support the clinician’s decisions regarding adaptive therapy. Digital ECMT will host and maintain an instance of the ACUITY tool for the DyNAMiC study team to use in 2022.

> “I have been delighted to be able to help design and run the first Carcinoma Unknown Primary (CUP) molecular tumour board meeting in collaboration with dECMT using eTARGET as the platform. This monthly meeting brings together CUP experts from across the UK to discuss patient cases, incorporating genomic alterations as part of the CUP-COMP study. The feedback from Investigators has been overwhelmingly positive.”

Dr Natalie Cook MD PhD
Honorary Consultant in Medical Oncology and Senior Clinical Lecturer. Experimental Cancer Medicine Team (ECMT). Manchester Experimental Cancer Medicine Centre (ECMC) Clinical Lead. Division of Cancer Sciences I Faculty of Biology Medicine & Health | The University of Manchester

2021 news and research activities

Title/Event	Type	Location	Date
Publications			
Research Evaluation Alongside Clinical Treatment in COVID-19 (REACT COVID-19): an observational and biobanking study	Publication	BMJ Online	January
Longitudinal characterisation of haematological and biochemical parameters in cancer patients prior to and during COVID-19 reveals features associated with outcome	Publication	ESMO Open	February 2021
Technology clinical trials: Turning innovation into patient benefit (DOI: 10.1177/20552076211012131/ ID: DHJ-20-0147.R2)	Publication	Digital Health	April
An explainable algorithm for detecting drug-induced QT-prolongation at risk of torsades de pointes (TdP) regardless of heart rate and T-wave morphology	Publication	Science Direct	April
An adaptive, biomarker-directed platform study of durvalumab in combination with targeted therapies in advanced urothelial cancer (BISCAY)	Publication	Nature Medicine	May
Encoding Explanatory Knowledge for Zero-shot Science Question Answering	Publication	International Conference on Computational Semantics (IWCS) Cornell University	May
Encoding Abstractive Knowledge for Zero-shot Science Question Answering, 14th International Conference on Computational Semantics (IWCS) 2021 (Full Paper/Research Track)	Publication	Association for Computer Logistics Anthology	June
NLP paper: Architectures of Meaning, A Systematic Corpus Analysis of NLP Systems	Publication	arXiv * Open-access repository	July

* arXiv Publications open-access repository of electronic preprints and postprints approved for posting after moderation, but not peer review.

Title/Event	Type	Location	Date
Publications			
NLP paper published at EMNLP - What is SemEval evaluating? A Systematic Analysis of Evaluation Campaigns in NLP	Publication	Proceedings of the 2nd Workshop on Evaluation and Comparison of NLP Systems	November
Wave comparisons of clinical characteristics and outcomes of COVID-19 admissions - Exploring the impact of treatment and strain dynamics	Publication	Journal of Clinical Virology	November
Home-based Digital Assessments with Applied Sentiment & Emotion AI Capture Improved Quality-of-life in Asthma Patients	Publication	Engineering in Medicine & Biology Society (EMBC)	November
Posters			
The digital ECMT cancer trial finder: computational support for cancer trial matching	Poster	GM Cancer Week Conference	May
NOTION: iN-home sampling Of cyTokines in ImmunOtherapy patient's	Poster	GM Cancer Week Conference	May
Assessment of the environmental impact of clinical trials	Abstract/ Poster	NCRI Online Conference	November
Focus group			
Online instructions for Technology Trials To understand patients' perceptions of providing online instructions only for applications to be used in technology trials.	Online Focus group	Zoom call	September

2021 news and research activities

Title/Event	Type	Location	Date
Conferences/Workshops/Presentations			
Cancer Drug and Development Forum Spring Conference 2021 (Current and future challenges of innovative oncology drug development) Digital Tools and AI in Oncology drug development	Donal Landers -Keynote lecture	CDDF Virtual Conference	February
ETARGET and Trial Finder demonstration to Precision Medicine Scotland	Presentation	Online	February
ECMT at The Christie event – Understanding Clinical Trials	Presentation / panel	Online	April
Presentation within 'Faculty of Biology Medicine and Health Social Responsibility and Public Engagement PPIE celebration event' – Patient engagement for digital ECMT	Presentation	Online	June
CORONET; COVID-19 in Oncology evaluatiON Tool: Use of machine learning to inform management of COVID-19 in patients with cancer.	Abstract presentation	American Society of Clinical Oncology (ASCO) Online	June
Cancer Drug Development Forum Workshop – Digital Tools and Artificial Intelligence in Oncology Drug Development Keynote lecture: Applying AI in Clinical Drug Development. Presentations: Endpoints Using Digital Tools, Design and Delivery of the IN-HOME study, Patient engagement in designing the clinical studies.	Donal Landers -Keynote lecture **Presenters:** Donna Graham, Leanne Phillips, Leanna Goodwin.	CDDF Virtual Conference	September
Greater Manchester Cancer Podcast: Leanna Goodwin spoke to host Steve Bland about her motivation to work as a Research Practitioner as part of digital ECMT and Experimental Cancer Medicine Centre (ECMC) Manchester	Podcast	Online	December

LINKS – group Websites and Tools

1. UpSMART website

Primary source of information for the UpSMART consortia providing details of the Accelerator Award and information on the Digital Healthcare Products (DHPs). Updated as and when new products become available.

https://upsmart.digitalecmt.com

2. ACUITY*

More information on the ACUITY* clinical trial visualisation and analytics tool on the UpSMART website (this has been developed to an open-sourced version).

*ACUITY is the name of the tool previously known as REACT.

https://upsmart.digitalecmt.com/?page_id=7

3. CORONET

COVID-19 risk in Oncology Evaluation Tool - **https://coronet.manchester.ac.uk/**

4. Digital ECMT Cancer Trial Matching Tool

Trial Matching software to support clinical decision making – matching a cancer patient's tumour genetic profile to optimal clinical trials, supporting our precision medicine research.

https://trialmatch.digitalecmt.com

5. CCE-DART

CCE_DART (cce-dart.com)

6. iMATCH Consortium

iMATCH - Innovate Manchester Advanced Therapy Centre Hub • ATTC Network - Advanced Therapy Treatment Centre (theattcnetwork.co.uk)

7. eTARGET

https://upsmart.digitalecmt.com/?page_id=229

8. P1PO

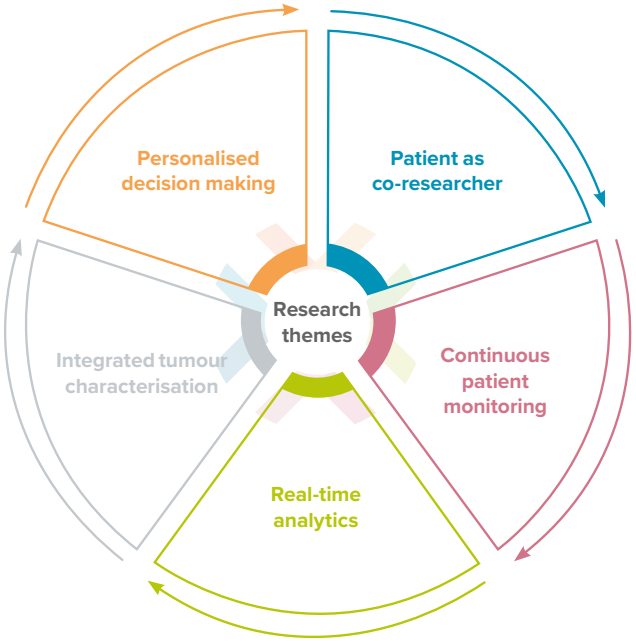
https://upsmart.digitalecmt.com/?page_id=852

9. GitHub repository for digital ECMT code

https://github.com/digital-ECMT

digital ECMT – 2021 report – 2021 news and research activities

Contact us



> “The digital ECMT continue to push the boundaries regarding the conduct of clinical trials, bringing new digital tools to support patient treatment decisions, and critically, involving the patient as a researcher in their own trial – progress this year has been stellar.”
>
> **Prof Caroline Dive CBE, FMedSci**
> *Interim Director CRUK Manchester Institute (MI) and Director CRUK MI Cancer Biomarker Centre and PI on the UpSMART Accelerator Award*

We work together in partnership to transform decision-making and the patient’s role.

If you are interested in collaborating with us in research under any of the themes on the left, please contact us.

Lets work together!

To get in touch
please contact us at info@digitalECMT.org

www.digitalecmt.org

digital Experimental Cancer Medicine Team

@digital_ECMT

digital ECMT – 2021 report – Contact us

Notes

Digital
Experimental
Cancer
Medicine
Team