Introducing the DIGital Institute for Cancer Outcomes REsearch "DIGICORE"

Digicore Board of Directors and Commercial Research Manager

After almost two years incubation time, early in April 2021 a new Organisation focused on producing cancer real world evidence, came into legal being – the DIGital Institute for Cancer Outcomes REsearch (DIGICORE). Like the Organisation of European Cancer Institutes, DIGICORE is set-up as a European Economic Interest Grouping with 18 prominent cancer centres and 2 cancer networks (UNICANCER and Alleanza Contro Il Cancro) as Members. A strategic partnership with the OECI is part of DIGICORE agenda. DIGICORE's objectives are to help prepare members for the digital revolution that will transform research through the routine use of electronic health records (EHR) and molecular diagnostic information (MDX) for trial automation, outcomes research, digital diagnostics and care quality management.

Two commercial partners have joined this ambitious endeavour: IQVIA, the leading contract research organisation and Illumina, the global leader in DNA sequencing and bioinformatics. These commercial parties have been chosen to ensure medical hypothesis neutrality. We believe this is an important principle and differentiator for DIGICORE when compared to pharma sponsored networks. IQVIA and Illumina also have the size, technology solutions and research experience to help set-up DIGICORE and support cancer centre members across Europe on their journey towards digital outcomes research.

This article lays out the scientific rationale and constitution for DIGICORE, the protections set-up for cancer centres that join and the benefits to cancer centres from becoming members or associate members. It will also provide some history and context to the new Organisation. Those themes and benefits to stakeholders are summarised below in Figure 1.

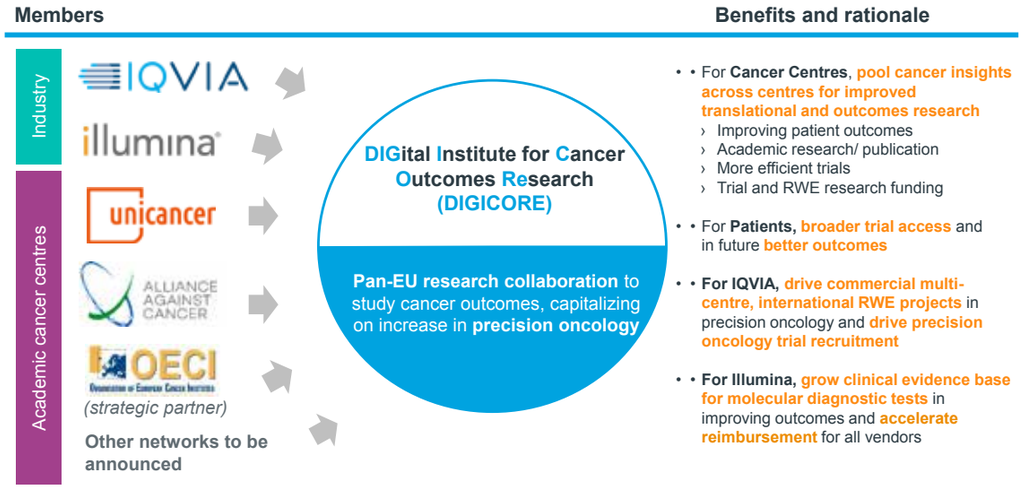

Figure 1: DIGICORE summarised

1. The scientific need for scale in cancer outcomes research

Cancer has seen an explosion of sub-types over the last decades as our increasing knowledge of disease aetiology leads to increasing specificity of classification. Initially this was by organ of origin, then by cell type, stage and grade and now by molecular subtype (especially somatic mutation subtype). This makes every cancer a rare cancer and places an emphasis on large scale collaboration.

Figure 2 illustrates this, using information from the Boston Tumour – Normal whole genome sequencing programme. It shows the rarity of most driver mutation events, and then asks a thought experiment to illustrate the rarity challenge - how big a country is needed to recruit a 250 patient cohort within 1 year with a given biomarker, for various cancers and biomarker frequencies, assuming all newly diagnosed patients can be recruited.

The results are challenging for existing research approaches, given most mutations occur in around 1% of patients or less. For a common cancer like lung, we would need all the patients in a large European country like the UK or France to recruit such a cohort. For a cancer like pancreatic (#10 ranked by incidence) we would need half of Europe, and for Liver (#20) almost every patient.

There are many challenges to achieving this scale, but a key one is cost. Traditional precision oncology cohort research is eCRF based and relies on costly re-type of clinical information and the research funding of molecular tests. We estimate costs for 10 cancers to get clinically relevant 100 patient cohorts on the 1% somatic mutations in each cancer at €0.5B to €1B using these methods[1]. This is clearly unaffordable.

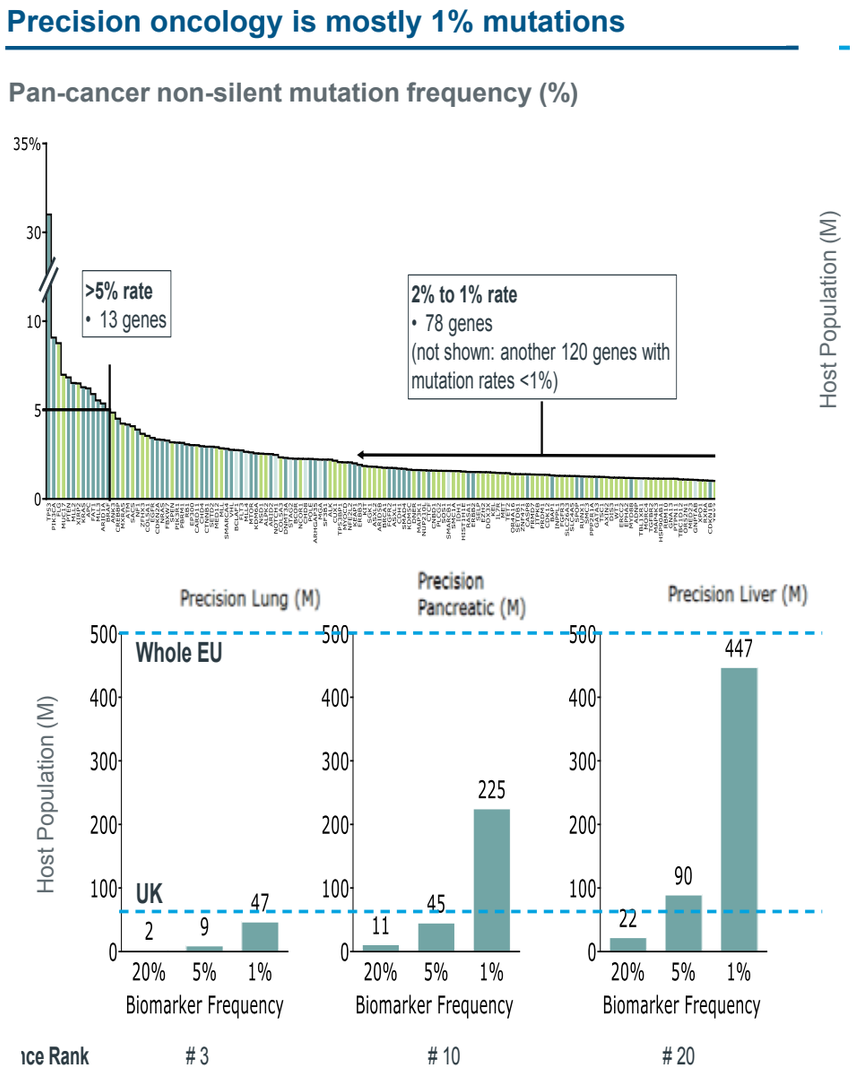

Figure 2: a thought experiment on precision oncology reproduced from Mahon & Tenenbaum 2015

However, if we can access similar information from routine care electronic health record, and avoid laborious re-type, we can transform those costs. We will also democratise research and trial access and allow more patients in need to access innovation. Clinical informatic[2] and bioinformatic[3] solutions are now coming of age and lie at the heart of the "digital" within DIGICORE.

By focusing on building an at-scale network, we will collectively get other benefits. Firstly, clinical variation in practice provides natural experimentation that can identify future best practice care. By having a larger network in academic comprehensive cancer centres like the OECI membership, we will see more of this clinically led innovation. In turn that can be validated in the DIGICORE network and cost-effectively rolled out to support national cancer plans. Secondly, we can develop and deploy digital care quality management tools – such as management analytics – that can help centres better drive guideline-based care into their practice. Thirdly, at-scale digital networks are highly desirable partners for both academic and commercial research in the precision era. We have interest from industrial partners in new forms of research, such as off-label observatories and using Mendelian randomisation to understand the impact of biomarkers in large panels on treatments that are not traditionally biomarker selected such as chemotherapy or radiotherapy. DIGICORE will provide its member centres the opportunity – but not the requirement – to participate in such exciting programmes of collaborative research.

2. Origins to DIGICORE

We can trace back the discussions that eventually led to the constitution of DIGICORE to the OECI Board meeting in Brussels, 2018. As this time, the OECI had already established its own working groups for outcomes research; IQVIA was exploring ways of partnering with European cancer centres to undertake real-world cancer research. A constructive dialogue ensued. This led to the recommendation to form a real-world research focussed new European Economic Interest Grouping (EEIG), where the main founding members would be cancer centres from across Europe. The new EEIG would be the legal vehicle for a public-private partnership to tackle outcome research.

DIGICORE FOUNDERS
1. ALLEANZA CONTRO IL CANCRO (Italy)
2. FONDAZIONE POLICLINICO UNIVERSITARIO A. GEMELLI IRCCS (Italy)
3. ISTITUTO EUROPEO DI ONCOLOGIA (Italy)
4. INSTITUT CURIE (France)
5. INSTITUT DE CANCEROLOGIE DE L'OUEST (France)
6. IQVIA (Belgium)
ASSOCIATE MEMBERS
1. UNICANCER (France)
2. CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD (France)
3. AZIENDA UNITÀ SANITARIA LOCALE DI REGGIO EMILIA IRCCS (Italy)
4. FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI (Italy)
5. FONDAZIONE IRCCS POLICLINICO SAN MATTEO (Italy)
6. HUMANITAS MIRASOLE SPA (Italy)
7. IRCCS ISTITUTO ROMAGNOLO PER LO STUDIO DEI TUMORI "DINO AMADORI" – IRST s.r.l. (Italy)
8. IFOM - THE FIRC INSTITUTE OF MOLECULAR ONCOLOGY (Italy)
9. ISTITUTI FISIOTERAPICI OSPEDALIERI (Italy)
10. OSPEDALE SAN RAFFAELE (Italy)
11. INSTITUTE OF ONCOLOGY LJUBLJANA (Slovenia)
12. MARIE SKLODOWSKA-CURIE MEMORIAL CANCER CENTRE (Poland)
13. MASARYK MEMORIAL CANCER INSTITUTE (Czech Republic)
14. INSTITUTO PORTUGUES DE ONCOLOGIA DO PORTO (Portugal)
15. UNIVERSITY CANCER CENTER FRANKFURT (Germany)
16. ILLUMINA NETHERLANDS BV (The Netherlands)

Table 1: DIGICORE Membership

The very purpose of establishing a dedicated "European research infrastructure" was to allow the joint-design of governance, technology and research operations by representatives of the cancer centres. Through a series of working sessions, the major strategic choices were agreed unanimously. These principles (see Section 3) covered topics such as the importance of each centre retaining absolute control over their data (achieved in part by data never being transmitted 'off site') and research/study participation. Over the course of several months, there was enthusiastic participation in these working sessions, which allowed the nature of DIGICORE to be shaped and clarified. Despite the emergence of the pandemic and its consequences (of which we are all aware) the momentum behind the project continued. In the 2nd half of 2020, the draft agreements were prepared to allow centres to review and formally decide on their preferred participation: Founding Member or Associate Member. Given the complexity of the project and the backdrop of COVID-19, it is a tremendous achievement to have reached agreement and officially formed DIGICORE on the 1st of April 2021! The membership of DIGICORE (See Table 1) remains open, similar to the OECI. DIGICORE is therefore open to any cancer centre interested in participating to the Grouping and endowed with data collection & management expertise.

The grouping is represented by its President (Prof Gennaro Ciliberto) and the Board of Directors (currently composed of Prof Mario Campone as Vice-President, Dr Sergio Maria Liberatore as Executive Secretary, Dr Xosé Fernández as Treasurer, and Prof Roberto Orecchia). Finally, a General Manager (Claudio Lombardo) ensures the day-to-day activities and manages the operating secretariat, reporting to the Board. Two research managers entrusted with academic and commercial programmes are in place. Dr Piers Mahon, from IQVIA, has been already appointed to cover the position of Commercial Manager. Finally, a General Assembly of all Members may be convened by the President. The DIGICORE General Assembly holds ultimate power to change the DIGICORE Board composition; the Grouping's by-laws; to approve the Balance and the Provisional Budget; to vote on new Member candidacies; and to take formal decisions when the finances of the grouping may be at risk.

3. Principle and protections for Cancer Centres

The guiding principles for the establishment of DIGICORE, its information governance and research operations have been unanimously agreed. An extremely important feature is the unambiguous centre-ownership and control over their local data. This is in part achieved by data remaining "on-site" and reinforced through DIGICORE's governance. As a consequence, research will be conducted via a federated analytic approach – the cutting edge of real-world data science. Given Illumina's role in DIGICORE, it is also appropriate to confirm that DIGICORE and its members are under no obligation to use central lab facilities or modify any aspect of their pathology labs and sequencing capabilities; neither is there any obligation to make use of software, terms or infrastructure that may be made available to DIGICORE.

Below is a set of principles agreed upon ahead of starting any legal drafting, which served as the 'blueprint' for the eventual formal contracts. In sum, they provide a powerful set of agreements as to how DIGICORE will operate as a collaborative partnership:

1. **Control**: Cancer centres are the only data custodians and controllers of their local data
2. **Study and Research Governance**: Each cancer centre decides independently if they wish to participate in any given study
3. **Economic Model**: DIGICORE's finances are regulated by the EEIG's statutes and 'fair market value' considerations on commercial studies (and funder rules for academic research)
4. **Common Operating Model for Research Execution**: for DIGICORE studies, centres will converge toward a common data model and common research practices over time; incoming funding will be used to build centres' local capabilities for research execution – there is no requirement on centres to reach a minimum standard on their own budgets. However, the technical standard of a centre will influence the research it can participate in

5. **Technical Infrastructure**: DIGICORE also expects to compete for EU funding with a view to reinforcing infrastructure locally, in line with an agreed DIGICORE technical architecture and common data model that is under development
6. **Information Governance**: centres will not incur additional costs for new systems or adaptations, however rigorous pseudonymisation is expected to be in place, and the information governance procedures and basis for research processing under GDPR of a centre may influence the types of research a centre can participate towards
7. **Inter-operability and pragmatic target datasets**: the evolution of research infrastructure needs to consider existing systems and software; existing electronic medical records systems have to be "research proficient", including with respect to GDPR and pseudonymisation. We will be pragmatic in how we approach this, prioritising data item sourcing and standardisation that are of the most importance to outcomes research. The work done in France to define the OSIRIS target data set provides an example[4]
8. **Funding the Establishment of the Entity**: members will contribute an annual membership fee to cover administration of DIGICORE; set-up costs were supported by IQVIA and over time we will expand funding by participation in collaborative bids
9. **Research Governance for unfunded research** (member proposed studies, no sponsor): this is an expected activity of DIGICORE, decision-making remains with individual members. Example projects pilot include multi-centre natural history studies in Ovarian Cancer and Multiple Myeloma, and the board is reviewing research priorities for other cancers[5]
10. **Governance of the Entity**: all EEIG members are equal, each having 1 vote[6]; collectively cancer centres have majority control; formal positions within DIGICORE academic research governance are to be held only by representatives from cancer centres.

	Bronze Centres	Silver Centres	Gold Centres
1. Precision oncology research maturity	**MDX testing below NCCN guidelines** • Testing almost all "IHC + some Sanger" • Very limited local precision expertise • Don't recruit to a Biomarker driven trials	**Testing at / above NCCN guidelines** • Small panel the norm only in NSCLC • Some but limited precision expertise • Recruit rarely for SoC biomarker trials.	**Large Panel MDX standard for all cancers** • Molecular tumour board pilots • Lots of precision trials underway, especially in "new biomarkers"
2. Routine clinical data digital research maturity	**No Data Warehouse, but core EMR exists** • Siloed Clinical Systems, very partial data • Unstructured Data often paper based • No Data Standardisation • Traditional eCRF studies only	**Basic clinically focused Data Warehouse** • Core Clinical Systems integrated • Identifiable Data, some standardisation • Unstructured Data is digital, un-mapped • Taking first steps in Database Research	**A research ready local Data Warehouse** • All cancer data in (chemo, radio, path), with strong master data management • Strong privacy norms (pseudo etc) • Do multi-site database research routinely
3. Pragmatic outcomes maturity	**Minimal routine outcomes in EMR** (death in hospital, ER admissions only) • Manual research processes established for date of death, but frequency of routine scans confounds rwPFS measures	**Outcomes interested but gaps remain** • Some communities of care track key outcomes, often outside of EMR • Progression only well tracked where easy to measure (e.g. CA125 in ovarian)	**Preparing for outcomes research at scale** • EMR captures progression and death • Experimenting with routine digital outcomes – PROs tools, AI on scans etc • Maybe pilots in liquid biopsy for relapse
4. Information Governance Maturity	**Not systematic on GDPR research reuse** • Very basic patient notifications on data, often limited to clinical use • eCRF processes use traditional pathways of study specific consent or national consent waivers	**GDPR foundations based on notification** • High Quality patient Notification and Opt-out process cover research • Database Studies have robust internal processes for release of aggregated data • Patient level data release requires consent or death	**Strong secondary use consents the norm** • Secondary consents routine, and provide a broad basis for research processing • Strong operational processes for privacy risk assessment and anonymisation, allowing appropriate anonymised patient level data release for research use

Figure 3 – Framework for the assessment of digital research maturity

Immediate focus – helping members prepare for digital research

The immediate focus for DIGICORE is to help its members to get ready for the era of digital research. We are a broad community and recognise that the digital maturity of cancer centres is highly variable. Given our belief in the need for scale, we anticipate programmes of work to help members prepare, as well as execute research. At the heart of this will be an honest assessment of our digital maturity so that we can better plan our collective research. Figure 3 provides a framework we are developing for that assessment. It has four main dimensions. Firstly, the availability of high quality, routine molecular diagnostic data. Secondly, the availability of high quality, integrated clinical information in common, pragmatic data models to both make data available for protocolised research and allow inter-centre digital interoperability. Thirdly, the availability of strong outcome data to turn activity data into science. Finally – and critically – strong information governance to allow the appropriate use of that patient information for research under GDPR and local information privacy laws.

There are centres on the Gold spectrum of this framework within DIGICORE. However, unlike other networks we will be extending a helping hand to less mature centres. This reflects our belief that the precision era requires scale, and to get scale we must work together to help everyone achieve a common standard. DIGICORE is as interested in helping the Bronze work towards Silver, and the Silver work toward Gold as it is in driving research between Gold centres. The only minimum standard is that a centre must have electronic health records and be interested in getting those records ready for research, funds permitting. We will be working with members to secure such funding. We are developing assessment tools to help centres understand their maturity and prioritise investment.

While funding will help develop the network, it is not essential to start doing research together. IQVIA's existing real world evidence networks have already shown that international real world evidence can be semi-automated without major IT investments. Instead, during protocol development a common data model can be pragmatically agreed between participants, and as records are extracted and curated, they can be converted to that model. This allows the development of common analytical R-scripts that can be shared between centres to automate cohort analysis. An example of this way of working is a recent 7 centre natural history study in ovarian cancer led by Prof. Geoff Hall at Leeds Teaching Hospital that is starting to read out and generate publications, without external funding. We will be looking to extend these expert collaborations to other cancers within DIGICORE after a board discussion on priority areas.

DIGICORE has started to map collaborative funding opportunities. Various members made their first joint submission in April, towards the CRUK – NCI Cachexia Grand Challenge.

Ultimately, DIGICORE wishes to play a strong role in the European Cancer Mission in the supply of large digital research cohorts and the digitisation of trial screening. We also wish to support the national cancer control plans with the supply of outcome and health systems research insights.

DIGICORE is open to establish formal collaboration with other sister cancer Organisations to build a common collaborative approach to these themes. We invite every cancer centre to join us on our mission to make "every willing patient a research patient and so transform cancer care".

1. *In each cancer we will need 10,000 patients to get 100 patients on key 1% mutations. For 10 cancers we need 100,000 patients. Costs per patient will be around €1000 to €2000 for a high quality panel test, and around €4000 to €8000 per patient for high quality clinical records, or a total of €5000 to €10,000 per patient.*
2. *The digital analysis of electronic health records*
3. *The digital analysis of molecular test results*
4. ***https://en.e-cancer.fr/OSIRIS-a-national-data-sharing-project***
5. *Protocols and more details are available on request from any OECI centre that is interested*
6. *The EEIG has two tiers of membership, which a cancer centre can select from. Members, with a vote and joint and several liability or associate members with no vote and no liability. For research activity, there is no difference in rights between the membership tiers.*