Workshop on histology independent drug development

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Disclaimer

- In the last 3 years I have received Honoria for attending advisory boards from Pierre Faber, Bayer, Novartis, BMS, Cybrexa, Ellipses, CV6 Therapeutics, Immunocore, Genmab, Astex Therapeutics, Medivir, and Sanofi Aventis.
- I have received honoraria for working as an IDMC member for Alligator Biosciences, GSK, Onxeo and SOTIO Biotech AG
- I have been paid for delivery of educational talks or chairing educational meetings by AstraZeneca, Novartis, Bayer and BMS.
- I have received funds to support attendance at conferences from MSD and BMS.

Scope

The main learning objectives from the workshop were

- To understand the current landscape of tumour agnostic drug development
- To be able to discuss suitable trial designs to deliver such studies
- To develop an understanding of biomarker development and need for tumour agnostic registrations
- To understand the regulatory environment around these registrations

SESSION 1: LESSONS LEARNED FROM PREVIOUS TRIALS – SUCCESSES AND FAILURES

Session chairs: Ruth Plummer (CDDF, UK) & Jaap Verweij (CDDF, NL)

Introduction / overview of successes
Alastair Greystoke (Newcastle University, UK)

Regulatory perspective
Elias Pean (EMA, NL)

Moving from experimental phase to evidence-based practice, a payer's perspective
Sahar Barjesteh van Waalwijk van Doorn-Khosrovani (CZ, NL)

Panel discussion
Moderators: session chairs, Panelists: speakers + Dr Steven Lemery (FDA, US)

Alastair Greystoke – key points from scene setting presentation

	FDA Histology Independent Licensed Therapies	Prevalent across malignancies	Activity across malignancies	Ease of diagnosis
Microsatellite instability	Pembrolizumab, Dostarlimab			
NTRK	Larotrectinib Entrectinib			
BRAF	Dabrafenib and trametinib		Except CRC	
RET	Selpercatinib			
FGFR			?	
BRCA 1/2				

Elias Pean – summary points from a regulatory perspective for success

EUROPEAN MEDICINES AGENCY

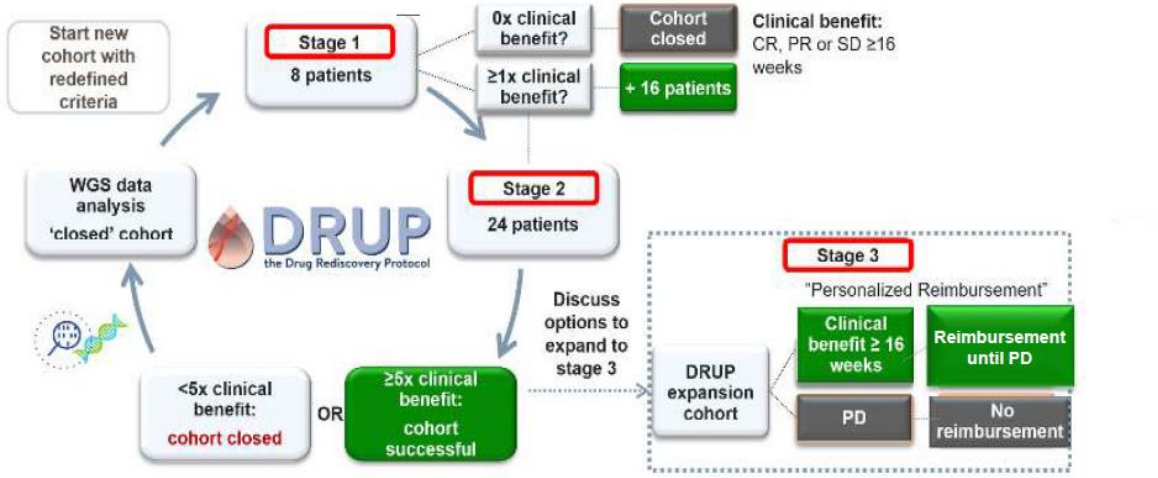
Successful histology independent development

- Requires **in-depth knowledge about the mechanism of action** and at least **strong plausibility of clinical efficacy** across subgroups;
- **Need to explore heterogeneity of effects** (interactions; resistance mechanisms) ;
- **Multiple therapeutic contexts, evidence of positive benefit-risk balance**
  - Higher chances of approval when high unmet need across subgroups
  - Challenging when competing against available options with established clinical utility (e.g. survival) in some subgroups; indirect comparisons (rare diseases; lack of historical data); extrapolation

Sahar BvWvDJ – highlights from DRUP study and need to integrate platform trials and data

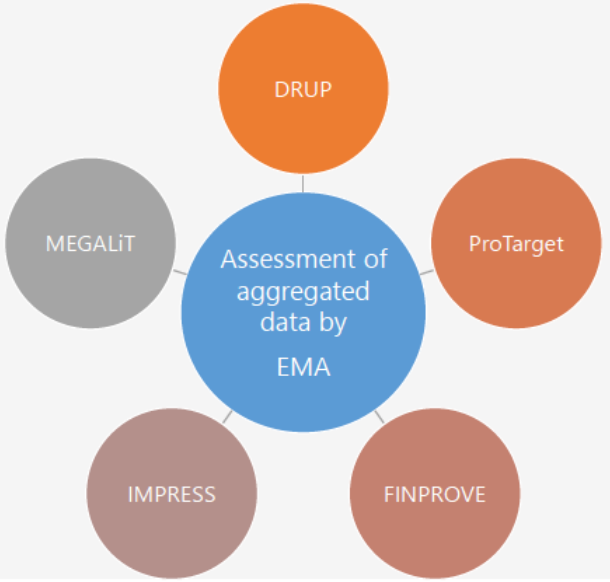
Drug Rediscovery platform

Metastatic cancer with actionable aberrations



Van der Velden et al, Nature 2019
Van Waalwijk van Doorn-Khosrovani et al., Ann Oncol 2019

Bridging the platforms of adaptive clinical trials



Adequate and rapid patient recruitment for ultra rare indications

Highlights of the Discussion

- Ideal trial endpoints and where in patient pathway such trials may come, and how they move up the pathway
- The challenges of overall survival as an endpoint, however it remains the best and most robust endpoint for regulators and payors of patient benefit
- Powerful advocacy from patient representatives in the audience over the importance of PFS as an outcome for patients

SESSION 2: BIOMARKER DEVELOPMENT AND OPTIMISATION

Session chairs: Brian Simmons (Roche, US) & Sacha Wissink (MSD, NL)

Scene-setting (in a forward looking way)
Sid Mathur (MSD, US)

Industry perspective
Lynn Brown (MSD, US)

Regulatory perspective
Hilke Zander (Paul-Elrich Institut, DE)

Evolution of comprehensive genomic profiling in precision medicine
David Fabrizio (Foundation Medicine, US)

Biomarker harmonisation: TMB case study
Jeff Allen (Friends of Cancer Research, US)

Panel discussion
Moderators: session chairs, Panelists: speakers

Sid Mathur – highlighting the "ingredients" needed and elegant illustration of how this was achieved with pembrolizumab

Lynn Brown and Hilke Zander – regulatory perspectives from US/industry and European

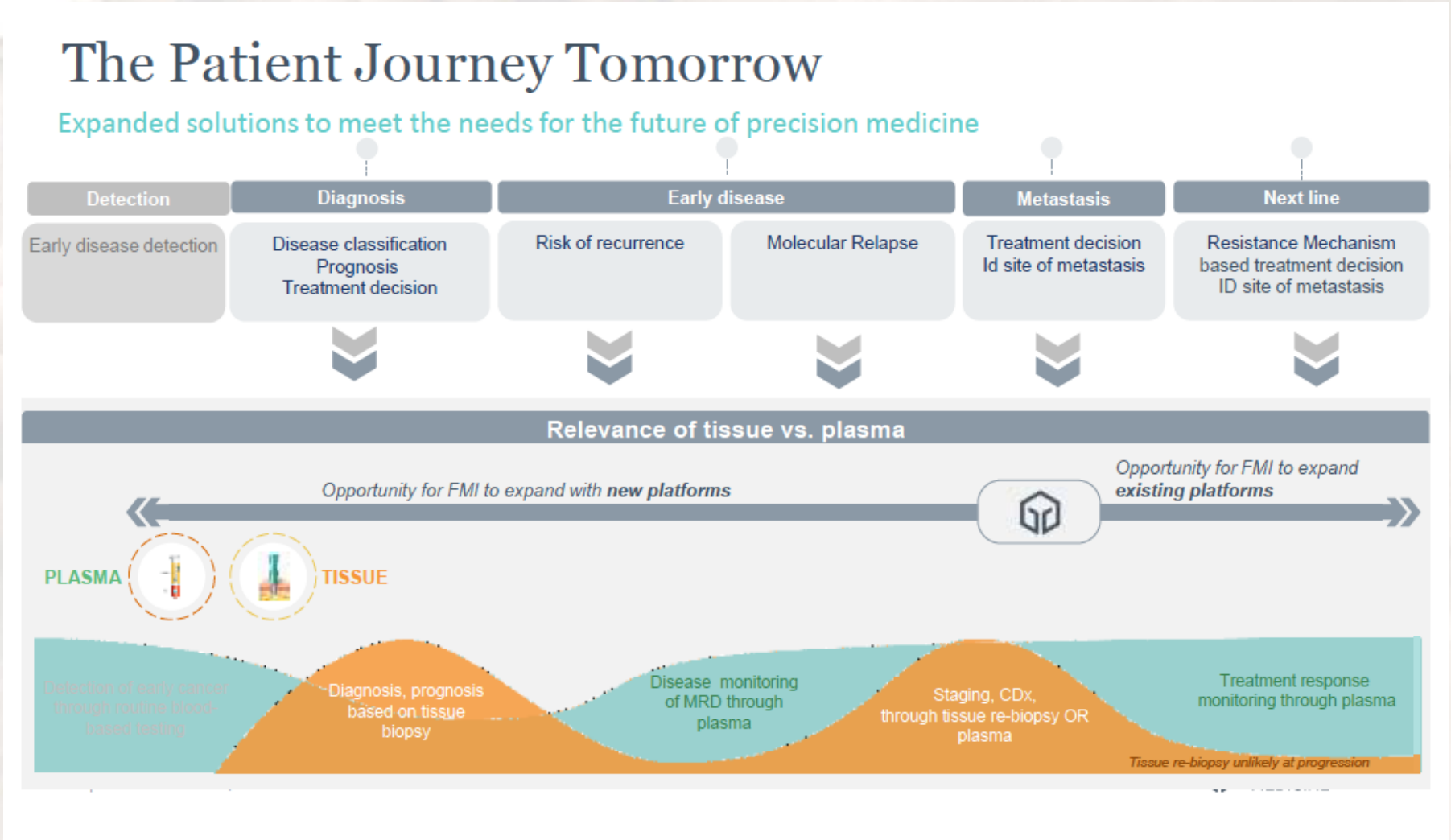
FDA Draft Guidance for Industry "Tissue Agnostic Development in Oncology" Issued October 2022

- Tissue agnostic drug development in oncology:
- Increased understanding of oncology disease pathways enables tissue agnostic drug development.
- Knowledge of biology of cancer and response to the drug necessary for effective tumor agnostic program.
- Tissue agnostic development can target:
  - Intrinsic alterations or receptors: NTRK (neurotropic receptor tyrosine kinase)
  - Factors extrinsic to the cancer: tumor microenvironment

European regulatory framework for CDx-based drug therapy

CDx: US (FDA)	CDx: Europe
Co-approval of a personalized medicinal product **(MP)** and a corresponding **specific CDx**	**Independent approval** of **MP** and corresponding **CDX** 2 different legal frameworks: IVD and MP regulation
CDx (trade name) is coupled via the **Full Prescribing Information**	**MP:** Drug approval / Biomarker section *MP and CDx not directly linked via SmPC* *Trade name normally not mentioned* **CDx:** Conformity assessment of the NB-(IVDR Article 48) *The name (INN) of the MP for which CDx is a companion test must be stated in the instructions for use (IFU) and Summary of Safety performance (SSP) for the CE-CDx*

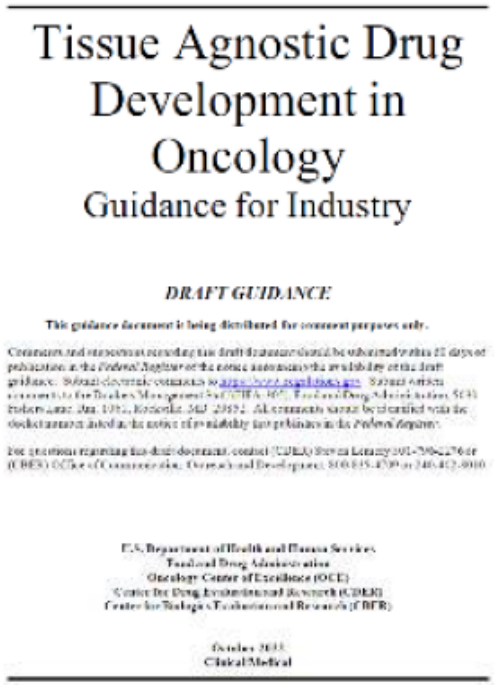
David Fabrizio – evolution of testing and a vision for an integrated future



Jeff Allen – discussed the TMB harmonization project and context of the new FDA regulations

Conclusions

- Tissue agnostic development may be a viable strategy for developing drugs that target specific molecular alterations across multiple cancers
- New regulatory guidance provides scientific considerations for determining if such an approach is appropriate and drug development processes
- To be successful several factors should be aligned in advance – e.g. scope of cancers included, determination of patient population, diagnostic performance



Tissue Agnostic Drug Development in Oncology

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

FRIENDS of CANCER RESEARCH

Highlights of the Discussion

- Practical aspects of validation process
- Challenges of working across industry sponsors to achieve this
- That validation of companion diagnostics remains essential for pivotal studies, and so assay considered “fit for purpose” in initial trials
- Key takeaways from discussion
  - Importance of some centralization during assay development for harmonization of results
  - Within Europe a clinical performance study will be required to achieve CE mark
  - Notified Bodies cannot give advice, EMA can, pathways in EU are quite tortuous with 60 day time line but multiple stakeholders to involve

SESSION 3: TRIALS DESIGN - BASKET OR UMBRELLA FOR OPTIMAL PROGRESS

Session chairs: Chitkala Kalidas (Bayer, US) & Alastair Greystoke (Newcastle University, UK)

Regulatory perspective
Dr Theodor Framke (EMA, NL)

Academic perspective
Prof Lucinda Billingham (University of Birmingham, UK)

Early phase side of drug development - Industry perspective
Richardus Vonk (Bayer, DE)

Panel discussion
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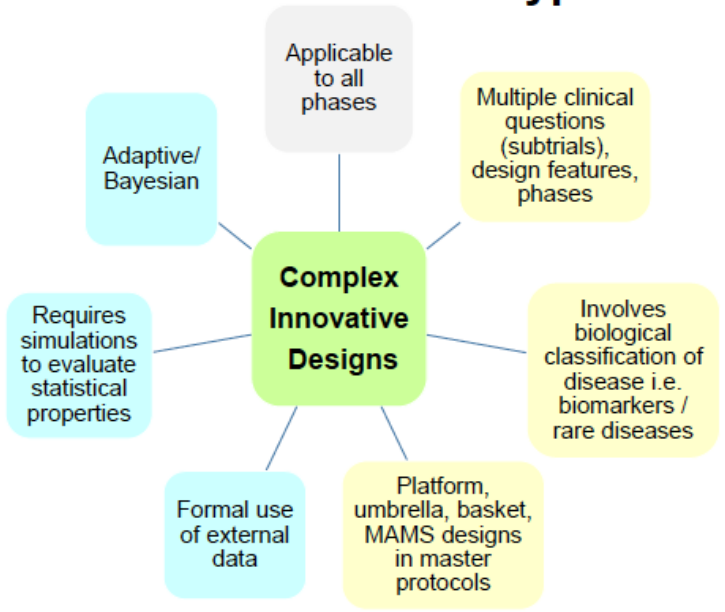
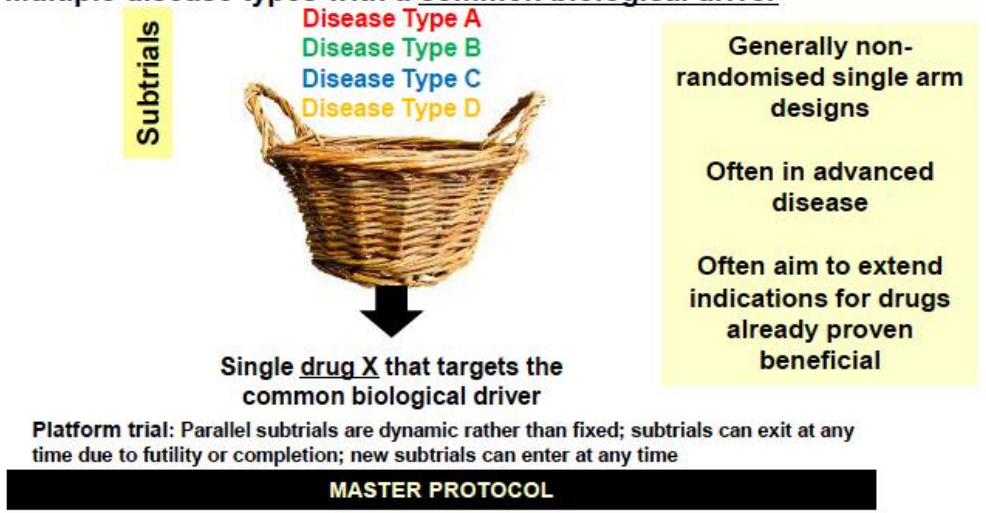
Cindy Billingham – complex innovative trial designs and adaptation within trial

Basket and Umbrella Trials: Types of CID



Basket Trials: Key Design for Histology-Independent Drug Evaluation

Multiple disease types with a common biological driver



Theodor Framke and Richardus Vonk provided regulatory and industry perspectives

- **ACT-EU initiative – Accelerating Clinical Trials EU**

- https://www.ema.europa.eu/en/news/accelerating-clinical-trials-eu-act-eu-better-clinical-trials-address-patients-needs

- Basket trials should answer 2 key questions – does the drug work and if it works when does it work (sup-type)?
- Common theme – importance of early statistical plan

Highlights of the Discussion 1

- Challenges of uncertainty over numbers and therefore modelling cohort size when costing a study
- Predicted time take to recruit can also influence decisions on cohort sizes, in particular in rare disease setting – consider specifying a minimum number
- Assessment of safety remains a key outcome, for licensed agents in novel settings as well as for novel agents and must be monitored
- What is an unmet need? – no available therapies or if better than available therapies may need to randomize. Usually considered by FDA based on efficacy parameters, can use a safety outcome but generally a higher bar

Highlights of the Discussion 2

- DETERMINE and DRUP studies – groundbreaking in this area but important to facilitate data sharing – to try and harmonise inclusion criteria where possible
- Bayesian design allows use of other data (even if inclusion criteria not a perfect fit) to estimate priors
- Decentralisation of trials may be needed for rare indications and this is being proposed by FDA
- EMA exploring use of RWD as contextuality and controls in single arm studies – will give scientific advice pertaining to this, although randomized approach remains preferred option
- Annals of Oncology paper on burden of bureaucracy in trials flagged to audience
- Overall take home “we need to get better at doing single arm trials”

SESSION 4: LEVERAGING THE POTENTIAL OF PRECISION MEDICINE: ENSURING EQUITY OF ACCESS TO PRECISION DIAGNOSTICS AND TREATMENTS FOR PATIENTS

Session chairs: Bettina Ryll (MPNE, SE) & Olga Valcina (Onco Alliance, LV)

Why equality and quality matters
Olga Valcina (OncoAlliance, LV, Deputy Director on Laboratory Matters, Institute of Food Safety, Animal Health and Environment "BIOR")

Genomic standards
Prof Eivind Hovig (University of Oslo, NO)

Distributed data governance - Addressing the precision public health dilemma
Philippe Page (The Human Colossus, SE)

Panel discussion
Moderators: session chairs, Panelists: speakers

Olga Valcina– highlighted the inequality of outcomes in EU and related these to healthcare spend and lack of harmonization of care standard

Cancer care gap between and in countries

- Affects Survival
- Worsens symptom burden
- Decreases willingness to pay
- Limits ability to adhere to an appropriate treatment plan
- Reduces public trust in the country and the healthcare system
- Increases stigma
- Reduces screening rates
  - why go for screening if there is no treatment in my country anyway

Normande

https://dairy-products-from-france.com/france-the-land-of-milk/dairy-cow-breeds-in-france/

We can harmonize farming, but cannot harmonize cancer care

Latvian Blue Cow

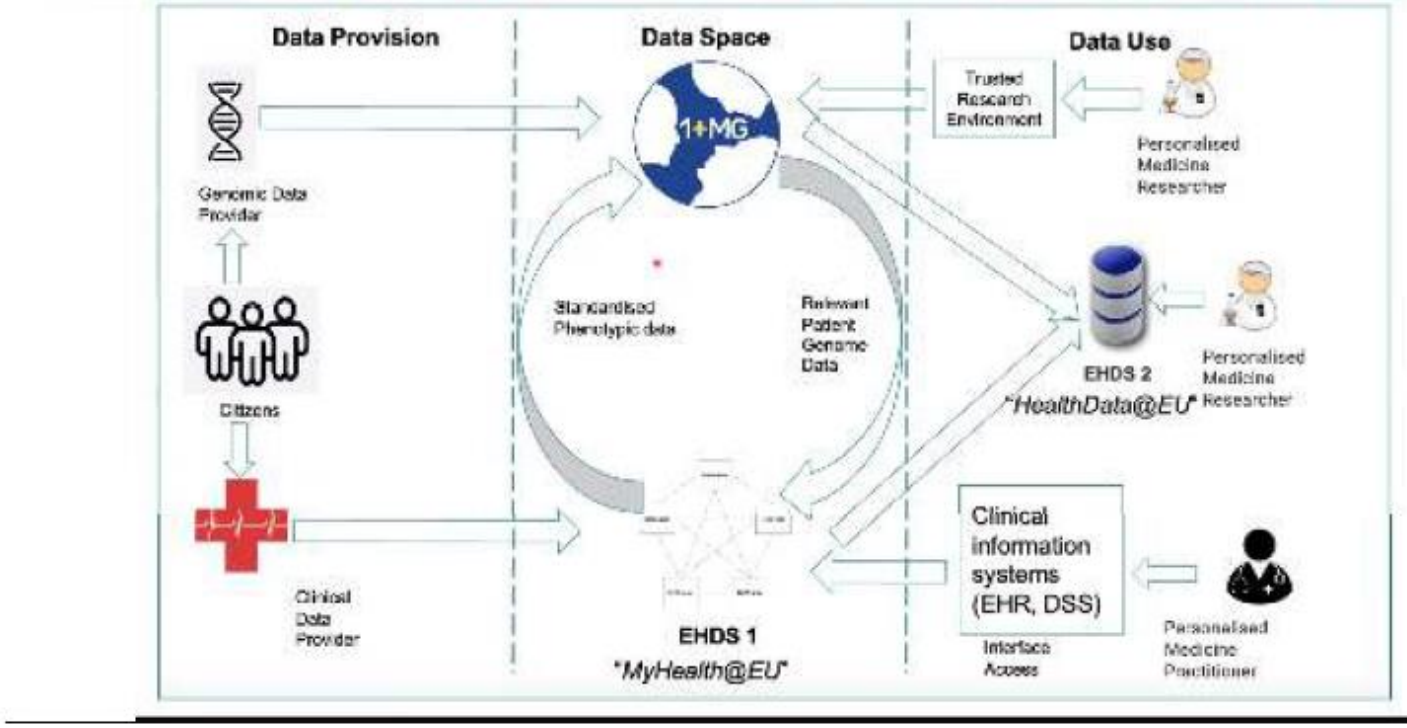
https://www.la.lv/vecauce-julija-beigas-jau-treso-gadu-notiks-govju-svetki

Belgian Red Cow

https://dairy-products-from-france.com/france-the-land-of-milk/dairy-cow-breeds-in-france/

Eivind Hovig – reviewed the initiatives and opportunities to connect data science and share for patient benefit

Connecting to the European Health Data Space

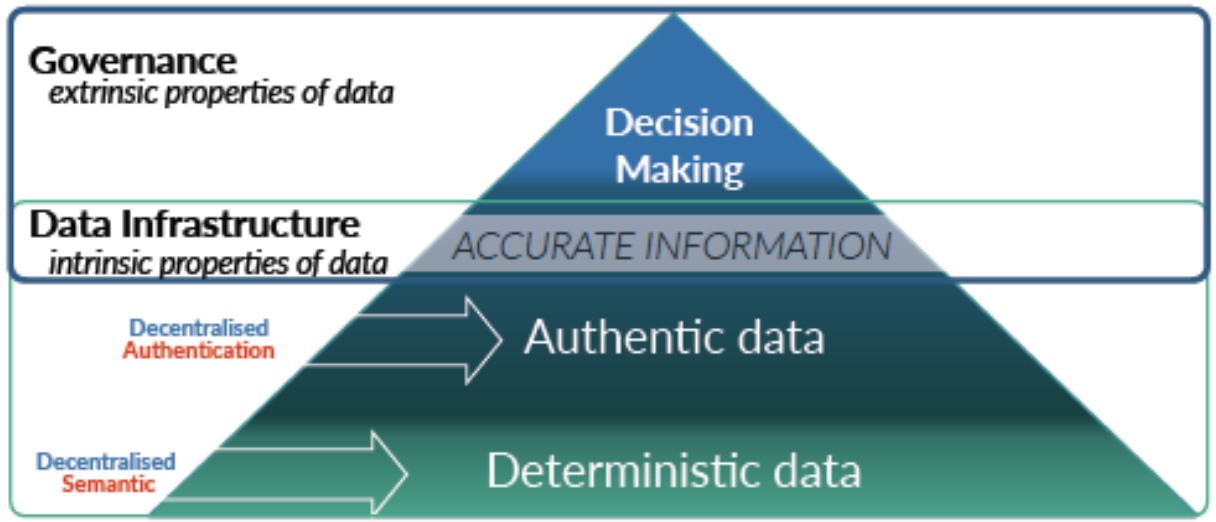


Philippe Page – importance of data governance to allow data sharing, needing hamonisation and decentralisation

The road to distributed governance

Operationalise Data Sharing at scale

Step 1 *Securing & Harmonising* data



Current concept of "platform" is replaced by traceable data (*data lineage* **)**

Decentralisation facilitates cross domain data sharing

Highlights of the Discussion

- Equality and equity of access to health services is a huge challenge with a major societal impact as well an individual impact in terms of burden of illness
- Barriers to equality of access include test standards and GDPR being not designed for health data sharing
- Good data governance is vital so participants sharing data trust the curators
- Sharing of data sets is a key step needed to improve equity of access to precision medicine

Take-home Messages

- Challenges
  - Single arm trials
  - Small cohorts
  - Certainty of data
- Common themes across sessions
  - Importance of biomarker development
  - Adaptive trial designs needed
  - Statistical input (early) vital
- Meeting report on CDDF website and white paper in preparation