Personalized Health and Related Technologies – A Program of the ETH Domain

Precision Medicine Research at Empa,

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Why Precision Medicine?

Why Precision Medicine?

- Is **personalized** medicine = **precision** medicine = **individualized** medicine = **stratified** medicine?
- Overall yes, the terms are usually used in a inter-changeable way.
- The concept of **personalized medicine is an old concept in medicine** as
  - It is said that Hippocrates highlighted already the need to adapt the therapeutics to particular patients "*it is important to know not which disease the patient has but which patient the disease has…*"
  - In general medicine, you need to consider the patient and his/her environment as a whole to treat correctly, for example:
    - Magistral prescription of drugs prepared by the pharmacist
    - Adapt a treatment to the capacities of patients (in/out-patient, oral or injectable…)

Need for reliability and precise biomarkers

- Importance of a **reliable & precise identification** by biomarkers:
  - Of course, critical for a medical decision for an individual patient, but all the more important when one wants to base statistical inferences for R&D purposes
  - Robust validation of biomarker
    - Different mutations in a specific gene associated with different responses to drugs: in **gastrointestinal tumors**:
      - mutation of **exon 11 of KIT gene** (coding for receptor tyrosine kinases and found on chromosome 4) associated with good response to

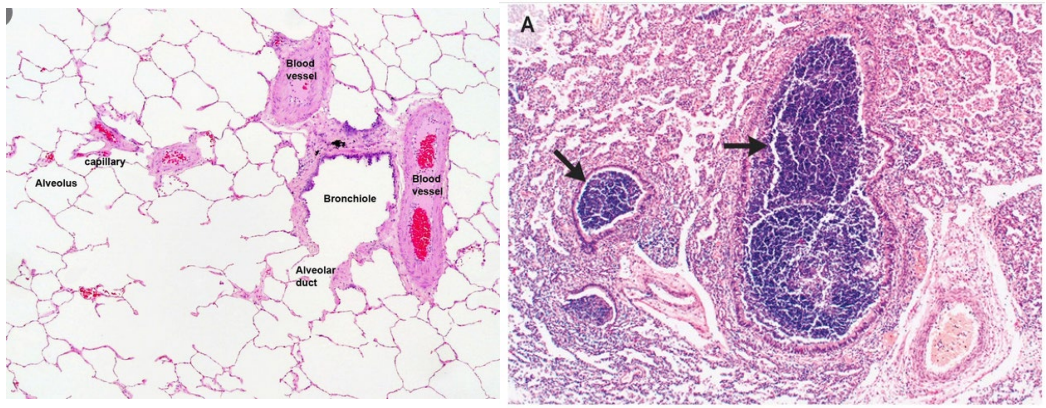
        400 mg of imatinib,
      - mutation of **exon 9 of KIT gene** requires

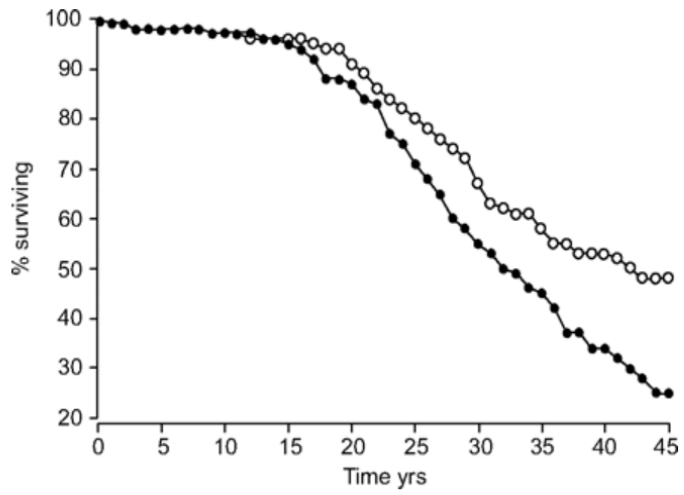
        600-800 mg of imatinib or

        sunitinib

Example of Precision Medicine success

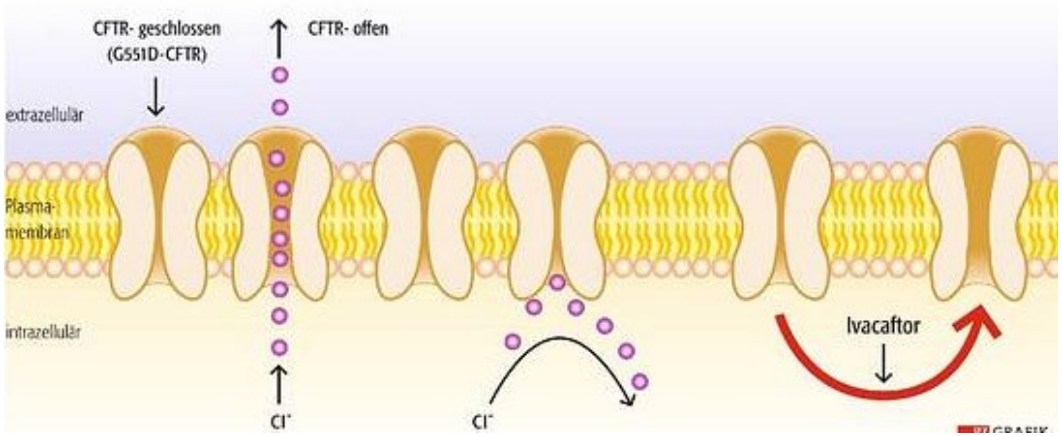
- **Cystic fibrosis**
  - Relatively frequent in Caucasian population; about 1/20 carrier
  - Mucus in various organs is thick and sticky:
  - In the lungs, the mucus clogs the airways and traps germs, like bacteria, leading to infections, inflammation, respiratory failure…
  - In the pancreas, the buildup of mucus prevents the release of digestive enzymes, resulting in malnutrition and poor growth
  - In the liver, thick mucus can block the bile duct, causing liver disease
  - Persistent coughing, at times with phlegm
  - Frequent lung infections including pneumonia or bronchitis
  - Wheezing or shortness of breath
  - Poor growth
  - Short survival

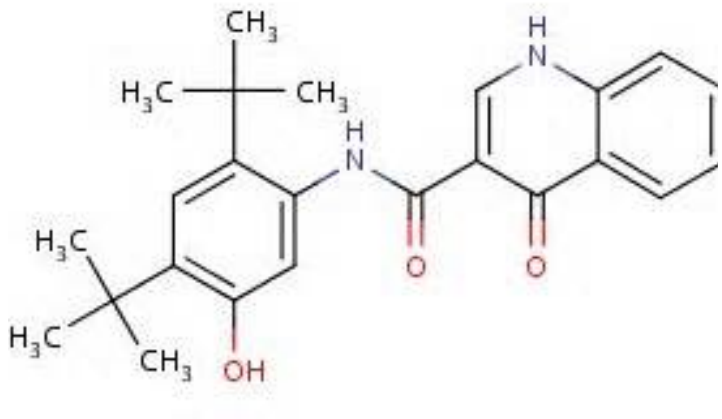




UK cystic fibrosis population by sex, 2003. ○: males; •: females.

Response prediction for a genetic disease: cystic fibrosis

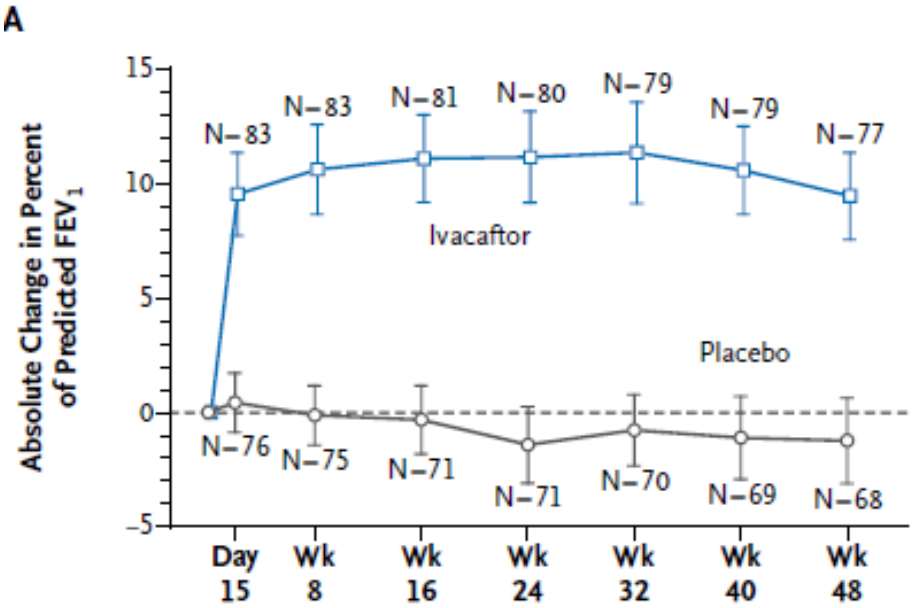




- Mutation in CFTR gene, mutation G551D is seen in 5% of patients
- Development of a small molecule, Ivacaftor, **increases time that activated CFTR channels remain open**

Patient genotype predicts response to drugs

- Kalydeco® (ivacaftor) was approved in 2012 by FDA with a "**priority review"**
- Only for patients with specific mutations in CFTR gene (in particular G551D) Only in 4-5% of patients Need for identifying these patients
- Further development of similar drugs which correct other mutations of CFTR
- Orkambi® (lumacaftor/ivacaftor) -> **F508del mutation (50-90% of the cases)**
- Symdeko® (tezacaftor/ivacaftor) -> F508del mutation + other mutations
- Trikafta® (elexacaftor/tezacaftor/ivacaftor) -> F508del mutation or one of 177



----------INDICATIONS AND USAGE----------

KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have one of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use. (1)

What is PHRT?

The four ETH / EPF institutions involved in PHRT

ETH Zürich

EPF Lausanne

Empa St. Gallen

Paul Scherrer Institut PSI Villigen

Strategic Focus Areas (SFA)

- In 2016, the ETH Board approved 3 Strategic Focus Areas (2017-2020)
- The three SFAs are approved for a second phase (2021-2024)

Strategic Focus Area
Personalized Health
and Related Technologies

Personalized Health and Related Technology (PHRT)

SDSC

Swiss Data Science Center (SDSC)

Strategic Focus Area
Advanced Manufacturing

Advanced Manufacturing (AM)

PHRT: frame and objectives

- The Strategic Focus Area “Personalized Health and Related Technologies (PHRT)” as defined in the **Strategic Planning 2017 - 2024** by the **ETH Board** will focus on core contributions of the ETH Domain institutions that are **complementary to the efforts** undertaken by other initiatives, such as the Swiss Personalized Health Network (SPHN)

- An important goal of the SFA is to allow **ETH Domain** institutions to be in a position to **collaborate** most fruitfully with **partners from SPHN** and with **international programs**.

PHRT: goals

- The overarching **goal** of the strategic focus area Personalized Health and Related Technology (PHRT) is to **establish and sustain the ETH Domain in a worldwide leading position** in the ongoing life science revolution that will ultimately transform medicine as it is today into '**individualized medicine**'.
- In essence a person's unique biological makeup and other patient-specific factors will guide decisions on how to maintain and restore health.

PHRT: the Network

PHRT: key points

- Program period: 2017-2020 ⇨ + 2021-2024 ⇨ **2017 - 2024**
- Budget: CHF 50 million ⇨ + CHF 50 million ⇨ **CHF 100 million**
- Funds awarded based on peer review; no institutional quotas
- Slim administrative structure

- **Executive Committee (EC)**
  - Bernd Wollscheid (chair), ETHZ*
  - Bart Deplancke, EPFL
  - Alex Dommann, Empa
  - Inge Herrmann, Empa
  - Gunnar Rätsch, ETHZ | SPHN
  - Elisa Oricchio, EPFL
  - Alessia Pica, PSI
  - Julia Vogt, ETHZ
  - Didier Trono, EPFL | SDSC | SPHN
  - Olivier Verscheure, Director SFA SDSC
  - Daniel Vonder Mühll, ETHZ
  - Damien Weber, PSI

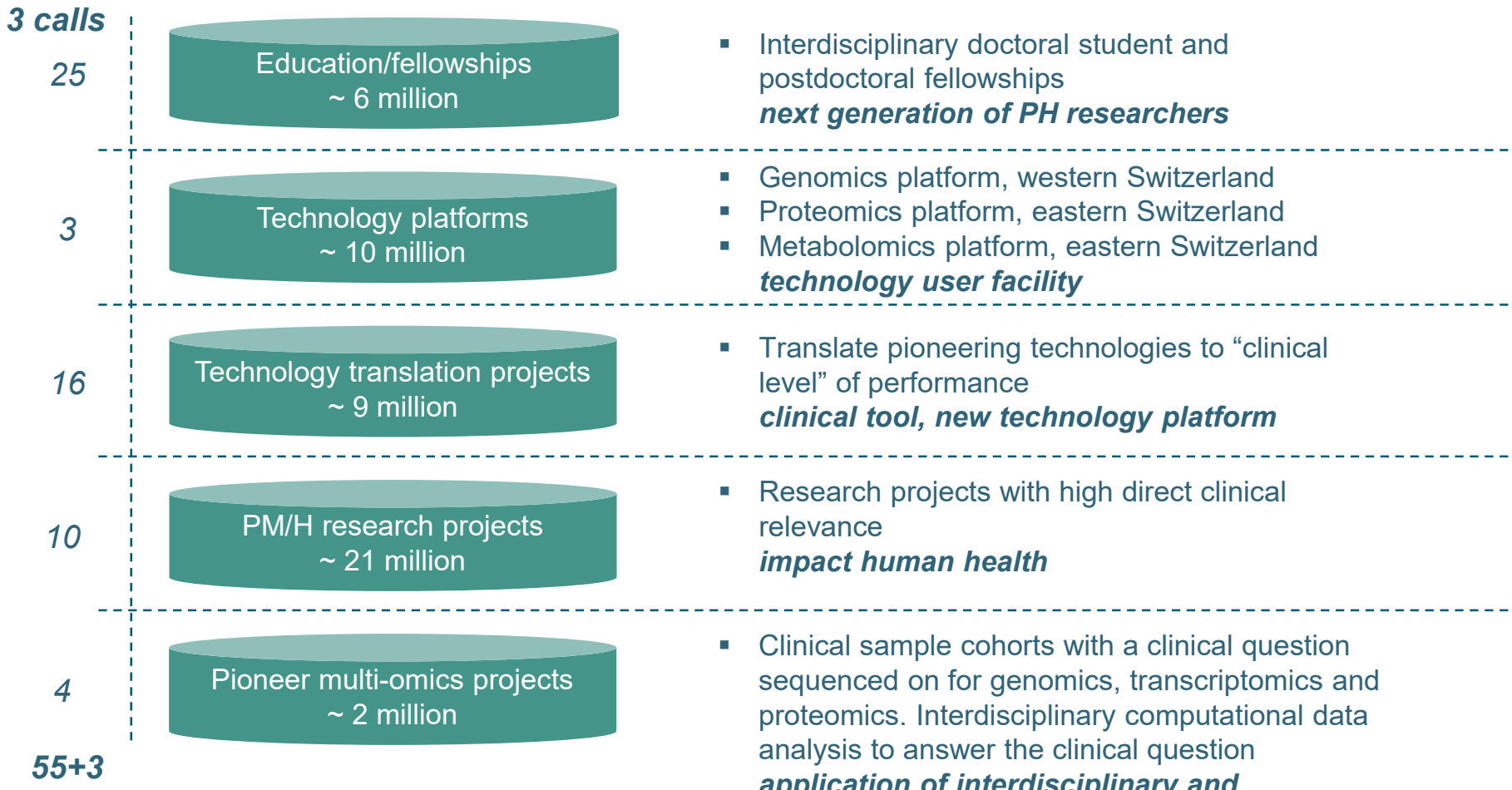
*Ruedi Aebersold until May 2019

- **Strategic Committee (SC)**
  - Detlef Günther (chair), ETHZ
  - Jan S. Hesthaven, EPFL
  - Christian Rüegg, PSI (Thierry Strässle)
  - Gian-Luca Bona, Empa

- **Administration / Office (3.5FTE)**
  - Daniel Vonder Mühll (Executive Director)
  - Francois Curtin (Medical Director)
  - Leoni Studer (Admin/Finances)
  - Vanessa Deppeler (Admin/Finances)
  - Rahel Hefti (Communication)

What has been done so far?

PHRT implementation: Project categories and numbers of the first phase (2017-2020)



Indications covered by PHRT projects

	Oncology & hemato-oncology	Neuro -logy	Metabolism & Obesity	Cardio-vascular	Bone	Infection and immuno-logy	Hepato -logy	Radio-logy/ Imaging	Surgery
No of projects	26	7	7	4	3	2	1	1	1
% of PHRT projects	50	13	13	8	5	3	2	2	2
% of Pubmed indication hits*	38	3	31	9	4	12	2	n.a.	n.a.

* over “precision medicine” hits in Pubmed

- Half of the PHRT projects are in **oncology or hemato-oncology**.
- **Neurology, metabolism/obesity, cardiovascular** and **bone** related projects are well represented
- Immunology and infections appears under-represented
- Imaging projects will increase after the 4th call

Orphan/rare diseases among PHRT projects

Orphan diseases (European definition: fewer than 5 people with the disease in 10,000 people) are represented with 6 PHRT projects (**12%**):

- P701: metabolic pathways of methyl malonic aciduria;
- P324 & P528: Ornithine transcarbamylase deficiency treatments,
- P329: arrythmia detection in a rare cardiac disease,
- P524: clip free method for uveal melanoma,
- P526: cell analysis in primary cutaneous T-cell lymphoma (de Sezary syndrome)

“Clinical evaluation” vs “Therapeutic application”

The projects have been categorized between:

“clinical evaluation”:

including biomarker identification, algorithms development for medical decision support or device supporting medical decision

“therapeutic application”:

New drug development or repositioning, development of biological therapeutic tools or devices to prevent or treat a disorder

	Clinical evaluation	Therapeutic application	Other
No of projects	44	7	1
Percentage	84.6	13.5	1.9

Patents

Evaluation based on the fact/intention to file a patent,

Possibly more projects may plan the filing opportunistically later

	Filed or planned patent	No patent
No of projects	10	44
Percentage	18.5	81.5

Two projects have already licensed their patents to industrial partners:

- Project P506 on protein **biomarkers for Parkinson disease** has licensed a patent to the start-up Biognosis AG
- Project P512 on **radiotracers for Alzheimer** disease and hypoxemia has licensed a patent to the pharmaceutical company Debiopharm SA.

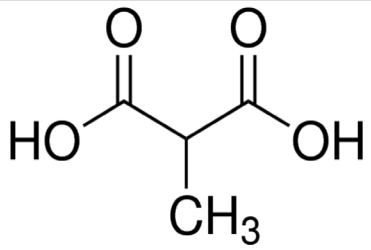
Collaboration with hospitals

The most frequent collaborations with hospitals are with **USZ** and **CHUV** followed by **Basel and Bern**

	Basel (USB)	Bern (Insel)	Geneve (HUG)	Lausanne (CHUV)	Zurich (USZ)	Aarau (KS)	Baden (KS)	StGallen (KS)	Sion (HC)
N	12	11	3	15	25	1	2	1	1
%	16.9	15.5	4.2	21.1	35.2	1.4	2.8	1.4	1.4

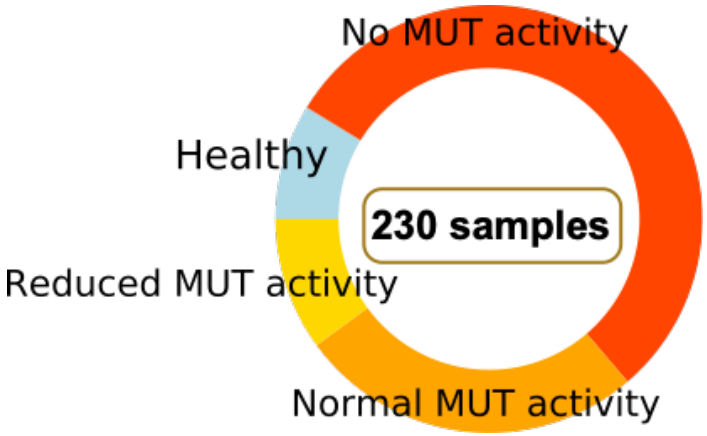
Realisation of large multi-hospital consortia is rare

Pioneer Project on MMA

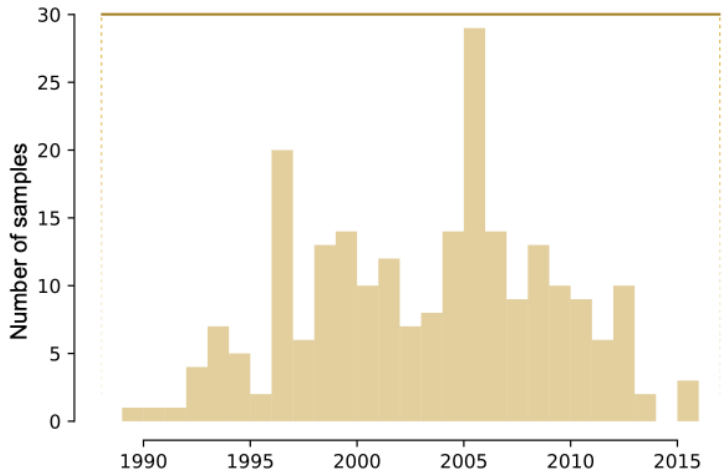


- **Clinical question:** Can multi-omic molecular profiles explain the disease mechanism of MMA and lead to improved treatment?
- MMA = Methylmalonic aciduria: a rare heritable metabolic disease linked to MUT gene
- **Samples collected from all across Europe** (Universitäts-Kinderspital Zürich, European Diagnostic reference center for MMA): 150 patient cell lines with mut-type methylmalonic aciduria; 60 patient cell lines with methylmalonic aciduria of unknown origin; 20 control cell lines

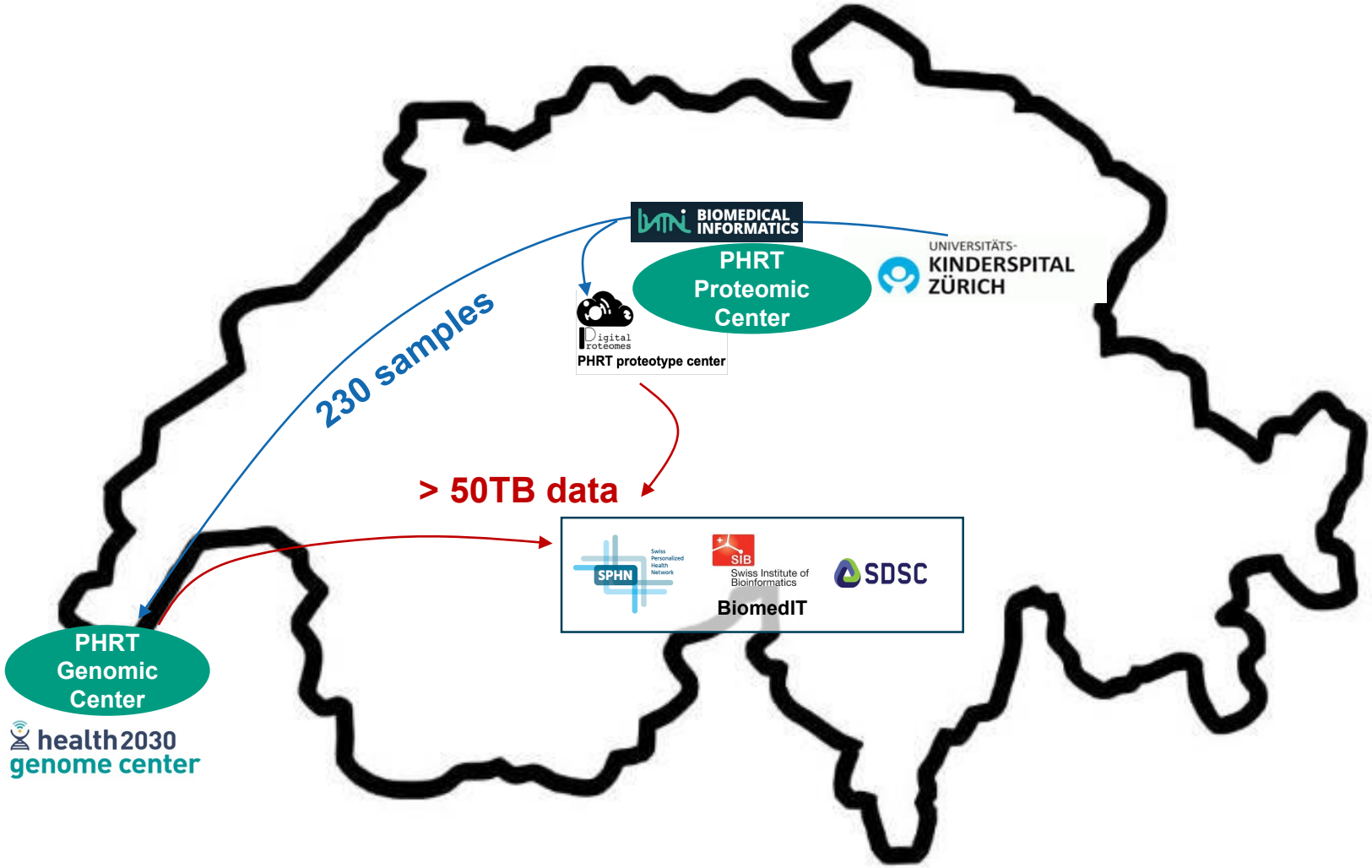
- **Sample cohort to address the question:**



- **Sample aliquots frozen over a 27-year period:**

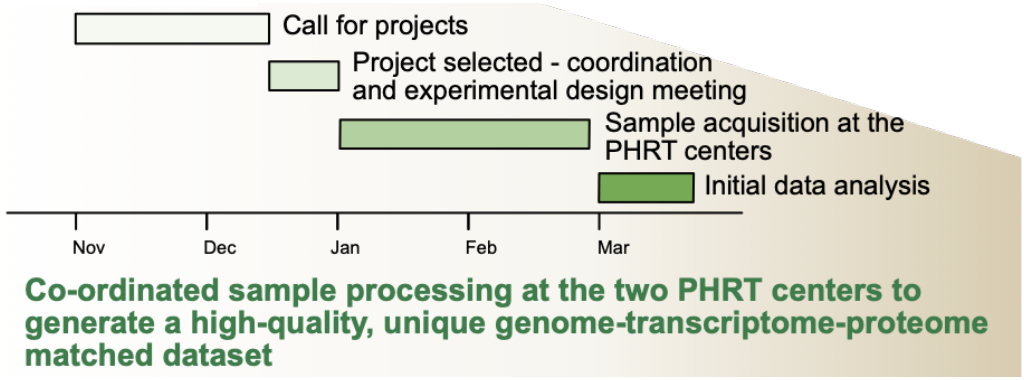


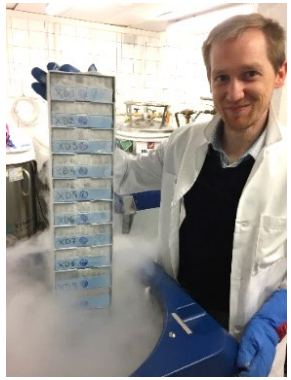
The technology platform system



«Technology Platform» **computational analysis.**
Meetings (in May 2019) with SPHN, DCC, BioMetIT

Pioneer Project: Procedure





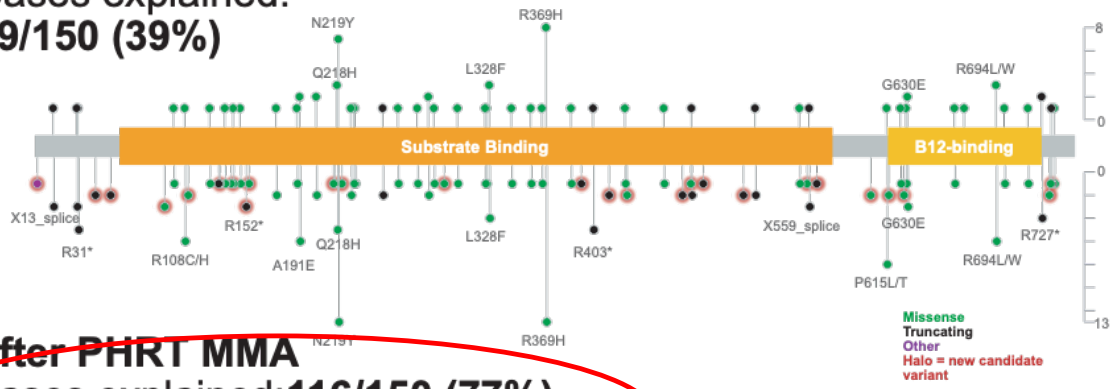
- **230 biospecimens subjected to coordinated**
  - Whole genome sequencing in Geneva
  - RNA transcriptomics in Geneva
  - Proteomics sequencing in Zurich
- **Data integration, data processing, data analysis**

This successful project triggered a call for pioneer project proposals (3rd PHRT call)

Pioneer Project: results

Before PHRT MMA
Cases explained:
59/150 (39%)

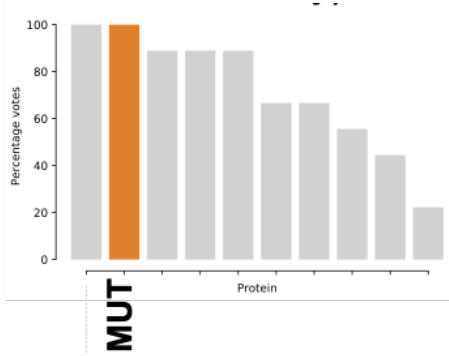
***MUT* variants in MMA cases**

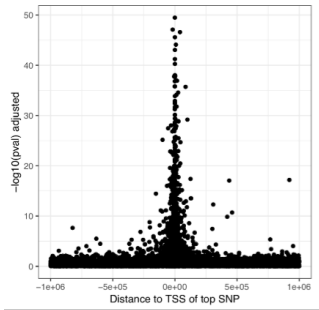


After PHRT MMA
Cases explained:**116/150 (77%)**
New candidate variants: 26

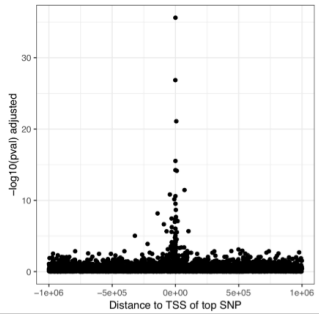
Genomics
Proteomics
Transcriptomics

Recapitulate existing knowledge and provide future leads to better explain disease mechanisms





Genome + Transcriptome
More than 2500 eQTLs



Genome + Proteome
More than 90 protein-QTLs

(Explanation by M. Baumgartner)

What is next?

Next Steps

- **Calls;**
  - 5th call just closed
  - National Data Stream with SPHN: call open since June 1st
  - 7th call in 2022
- **Swiss Multi-Omics Center** SMOC integrating the 3 platforms
- **Multicenter Imaging Hub** emerging from Pioneer Imaging Projects
- **Computational Hub** dedicated to health data analysis
- Continuation of the development and support to projects related to Personalized Health/Precision Medicine especially in view of t**esting new developments with clinical trials**

Thank you!

For any questions:

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