

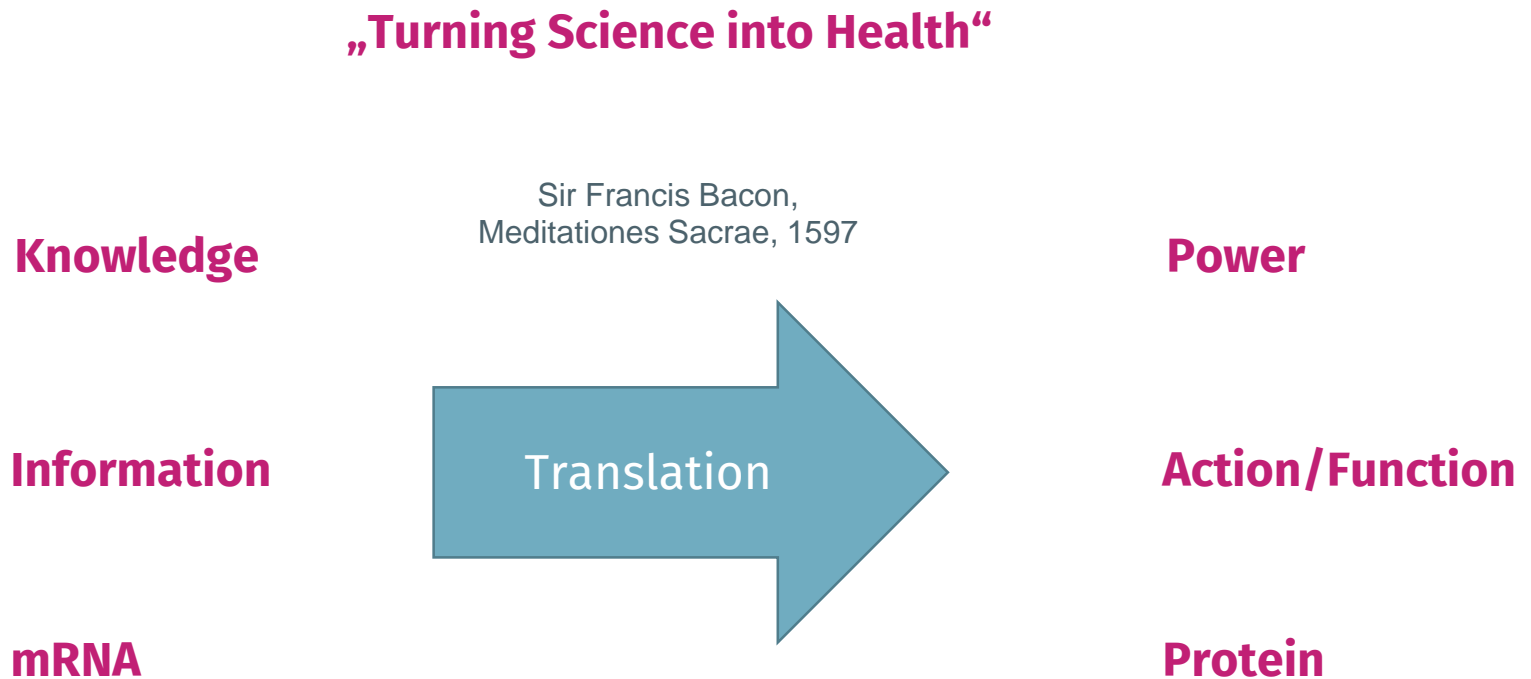
The BIH – an Institute Dedicated to the Science of Translation

Prof. Dr. med. Christopher Henrik Baum



Aus Forschung wird Gesundheit

What is Translation?



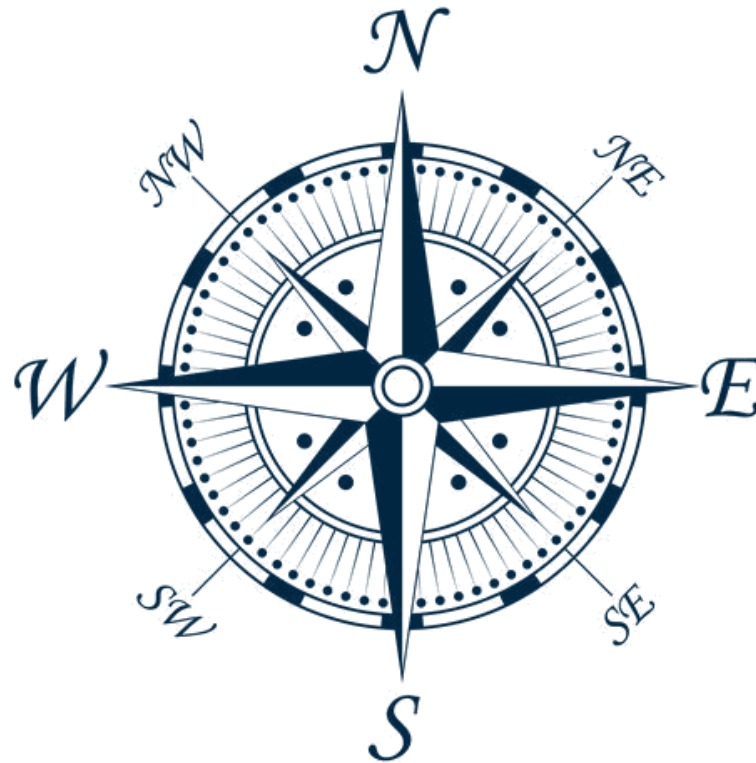
Navigation

Postground

effect of sustainable development

Background

Status quo



Foreground

future aims and
milestones → pathway

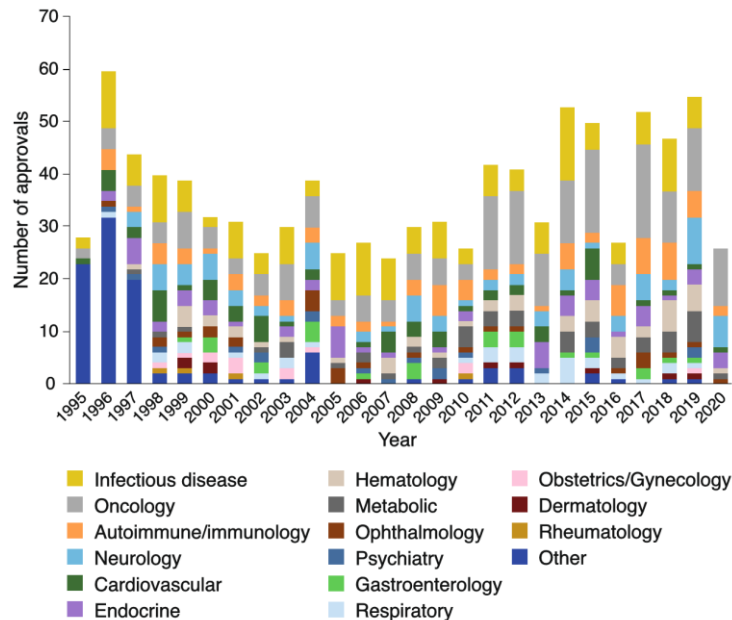
Sideground

may change perspective and speed of the process

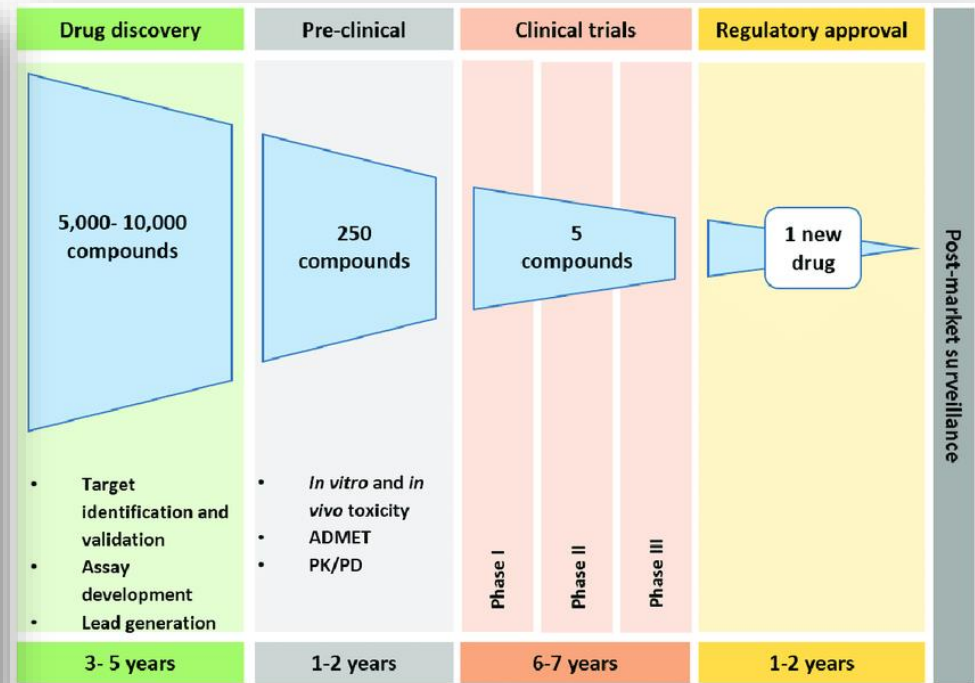
Background | Drug pipeline & bottlenecks

Historic US regulatory approvals by drug class

Despite the pandemic, the rate of drug approval looks remarkably similar to previous years.



Source: BioMedTracker, a service of Sagient Research (<http://www.biomedtracker.com>).



https://www.researchgate.net/figure/Drug-discovery-and-development-timeline-The-current-drug-approval-pipeline-can-take-15_fig1_308045230

Academia-driven

- ATMPs (gene & cell therapy, tissue engineering)
- Medical engineering incl. digital products
- Biomarkers (precision medicine)

Relevance | ATMPs and biotherapeutics



vfa. Die forschenden Pharma-Unternehmen

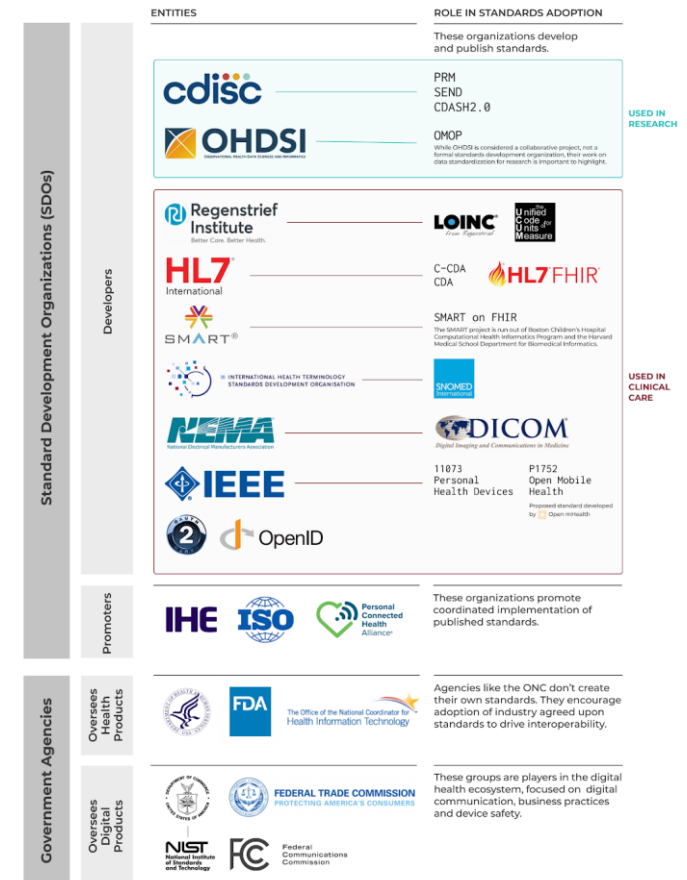
Relevance | Digital medicine

DIGITAL HEALTH			
		DIGITAL MEDICINE	
		DIGITAL THERAPEUTICS	
DEFINITION	Digital health includes technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes; capture, store or transmit health data; and/or support life science and clinical operations.	Digital medicine includes evidence-based software and/or hardware products that measure and/or intervene in the service of human health. ¹	Digital therapeutic (DTx) products deliver evidence-based therapeutic interventions to prevent, manage, or treat a medical disorder or disease. ²
CLINICAL EVIDENCE	Typically do not require clinical evidence.	Clinical evidence is required for all digital medicine products.	Clinical evidence and real world outcomes are required for all DTx products.
REGULATORY OVERSIGHT	These products do not meet the regulatory definition of a medical device ³ and do not require regulatory oversight.	Requirements for regulatory oversight vary. Digital medicine products that are classified as medical devices require clearance or approval. Digital medicine products used as a tool to develop other drugs, devices, or medical products require regulatory acceptance by the appropriate review division.	DTx products must be reviewed and cleared or certified by regulatory bodies as required to support product claims of risk, efficacy, and intended use.

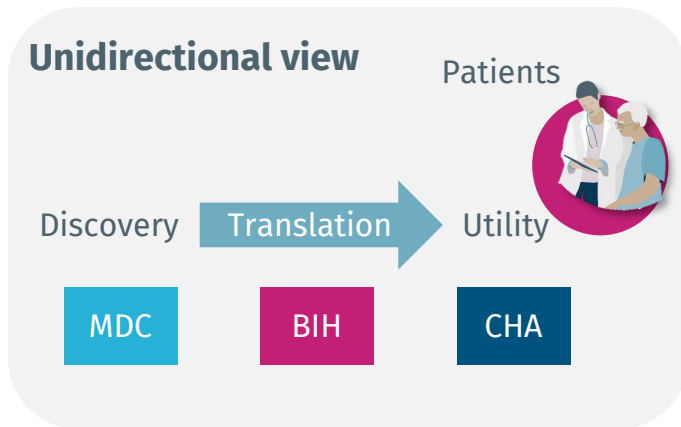
1 <https://www.dimesociety.org/index.php/defining-digital-medicine>
2 <https://www.dbaalliance.org/dtxproducts/>
3 It is important to check with local regulatory requirements in each jurisdiction the product is manufactured, registered, or used in.



STANDARDS AND KEY STAKEHOLDERS IN THE DIGITAL MEDICINE COMMUNITY

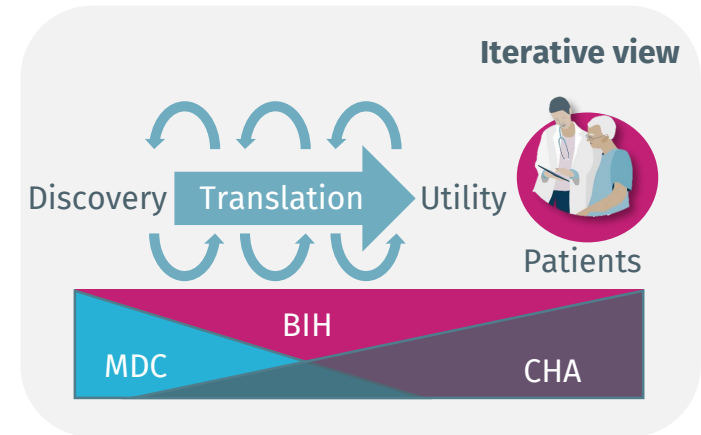


Foreground | The BIH – an institute dedicated to translation

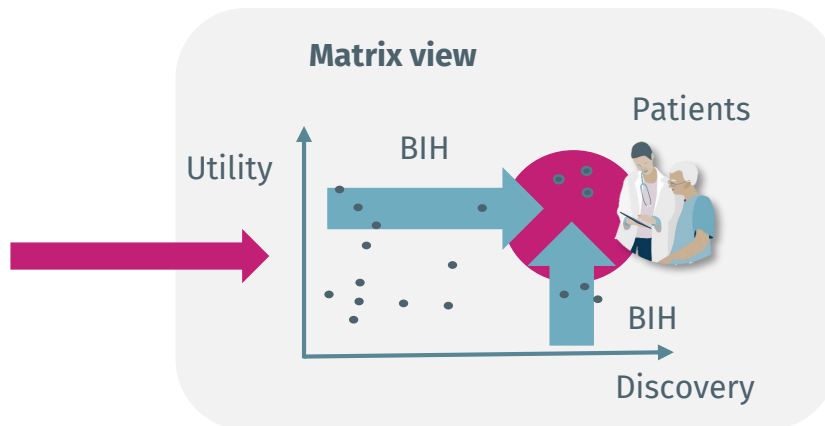


BIH to complete
the **ecosystem**
of MDC and
Charité

**Patient
orientation**



Scale ?
Metrics?
Use case?

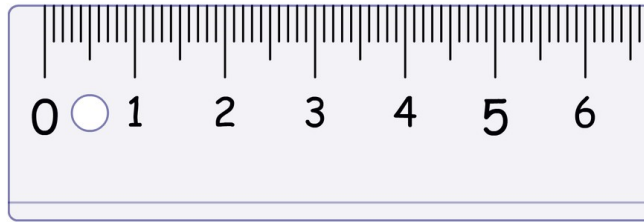


Mindset

Translation =

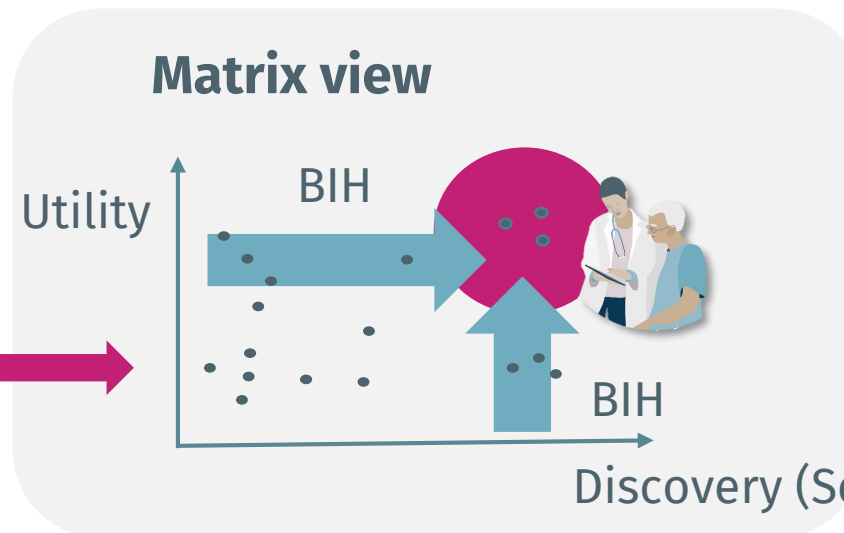
- *increasing discovery in utility-oriented development*
- *increasing readiness for utility in discovery-oriented research*

Developing translation as an *exact science*



- Medical need
- Patient outcome
- Economic value
- Readiness for application: TRLs
- Regulatory readiness
- Intellectual property
- Technical skills
- Uniformity, reproducibility
- Financial need, feasibility

Scale ?
Metrics?



Technology Readiness Levels (NIH)

TRL	Description
TRL1	Review of Scientific Knowledge Base
TRL2	Development of Hypotheses and Experimental Designs
TRL3	Identification and Characterization of Preliminary Product
TRL4	Optimization and Demonstration of Activity and Efficacy
TRL5	Advanced Characterization of Product and Initiation of Manufacturing
TRL6	Regulated Production, Regulatory Submission, and Clinical data
TRL7	Scale-up, Initiation of GMP Process Validation, and Phase 2 Clinical Trial(s)
TRL8	Completion of GMP Validation and Consistency Lot Manufacturing, Clinical Trials Ph3, and FDA Approval or Licensure

Objective Assessment

- Infrastructure
- Careers
- Teams
- Cooperations
- Products
- Projects
- Research and clinical landscape

Granularity OK

<https://ncai.nhlbi.nih.gov/ncai/resources/techreadylevels>

BIH Translation Agency to assess projects and identify partners

Precision mindset: Seneca

All wish *translation* (happiness), but are dull at perceiving exactly what it is that makes it work: and so far is it from being easy to attain to *translation* (happiness) that the more eagerly you struggle to reach it the further you depart from it, if you take the wrong road; when this leads in the opposite direction, your very velocity carries you all the further away.

We must therefore first define clearly what it is at which we aim: next we must consider by what path we may most speedily reach it, for on our journey itself, provided it be made in the right direction, we shall learn how much progress we have made each day, and how much nearer we are to the goal.

But as long as we wander at random, not following any guide except the shouts and discordant clamours of those who invite us to proceed in different directions, our short life will be wasted in useless roamings, even if we labour both day and night to get a good understanding.

L V C I I A N N E I S E N E C A E D E V I T A

beata ad Gallionem fratrem,

L I B E R V N V S .

C A P V T I .



IVERE, Gallio frater, omnes beatè volūnt, sed ad perveniendū quid sit, quod beatā vitam efficiat, caligant. Adeoq; non est facile consequi Beatā vitā, ut ab ea quisq; eo longius recedat, quo ad illam concitatius fertur. Si via lapsus est, quæ in contrarium ducit, ipsa velocitas maioris intervalli causa fit. Proponendum est itaq; primū, quid sit quod appetamus. Tunc circumspicendum est, quā cōtēdere illō celerrimē possimus, intellectu in ipso itinere, si modo rectum erit, quantum quotidie proficiamus, quantoq; propius ab eo simus, ad quod nos cupiditas naturalis impellit. Quandiu quidem pāsim vagamur, non ducem secuti, sed fremitum & clamorem dissonum in diuersa vocantium conteritur vitā inter errores, brevis, etiā si dies noctesq; bonæ mentis laboremus. Decernatur itaq; & quō tendamus, & quā, non sine pe-

A 4 rito

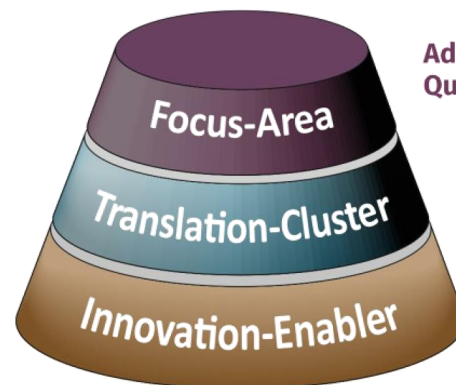
Science (~Wikipedia)

A system of knowledge, discoveries and experiences

- Systematically collected and taught, stored, expanded and passed on
- Causality and clearness: relationships, rules, terms and definitions, theories and hypotheses
- Methodology, measurement, quantification (exact sciences)

- Rational, objective, honest
- Reproducible, valid
- Transparent
- Definite, unambiguous
- New, reliable, useful

BIH



Address Burning Questions

Match Experts with Disruptive Technology

Generate a Translational Mindset

Projects Dynamic Selected

Support Stable Required

QUEST (est. 2017) - Quality Ethics Open Science Translation Center for Transforming Biomedical Research



QUEST abbr. Quality, Ethics, Open Science, Translation: Center of the Berlin Institute of Health.

...to increase the trustworthiness and usefulness of biomedical research – at BIH (i.e. Charité and Max Delbrück Center) and beyond – by optimizing its robustness, transparency, patient-orientedness, and ethics.

<http://quest.bihealth.org>

QUEST Approaches



- **Quality assurance:** promote compliance of preclinical and clinical research with standards and guidelines on design, conduct, analysis and reporting.



- **Education:** develop and implement training and teaching resources on experimental and study design, methods to reduce bias, new modes of publishing, open science, etc.



- **Open Science:** improve the accessibility and transparency of BIH research and its results through Open access and Open data.



- **Rewards and incentives:** develop, implement, and assess the impact of novel indicators incentives and metrics for rewarding researchers, appropriating funding and awarding academic degrees.

QUEST Approaches



- **Stakeholder engagement:** develop, support, and evaluate patient and stakeholder engagement activities throughout the entire process of biomedical research



- **Meta-Research:** identify opportunities for improving research practice and obtain evidence for the impact of its activities through 'research on research'.



- **Bioethics of translation:** develop scientifically sound and practice-oriented recommendations on ethical requirements for research with humans, animals and sensitive data

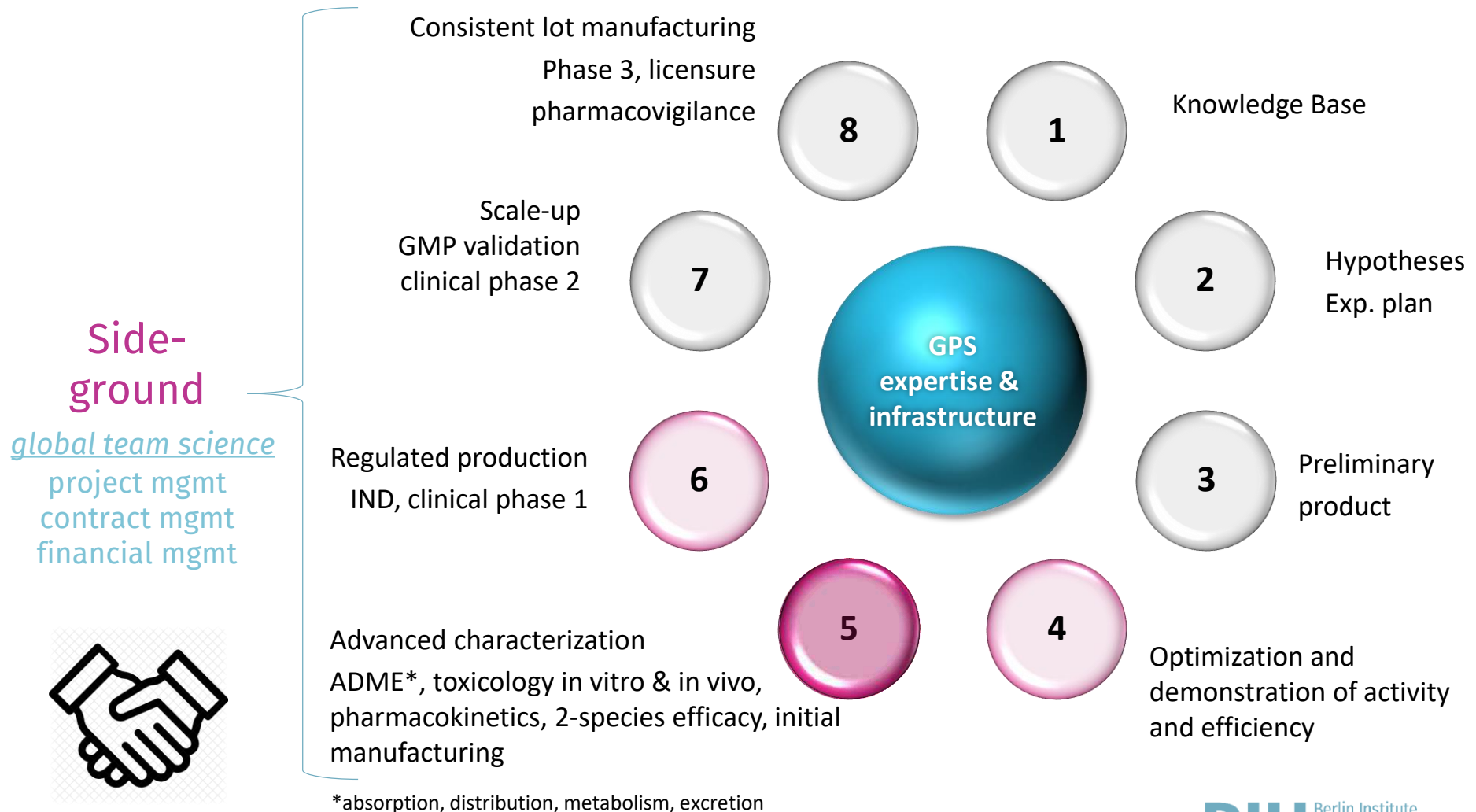


- **Think tank:** act as advisors to stakeholders in biomedicine from funders to politics.

BIH approaches to improve readiness for translation

BIH-Academy	<i>People</i>	Task Approach Incentives	Establish a faculty skilled in medical translation Support personal development and careers BIA - Career Support Initiatives
QUEST	<i>Quality</i>	Task Approach Incentives	Assure optimal use of material and human resources Define and assure value of research Value-Incentives (<i>VoM</i>)
BIH-Accelerator	<i>Support</i>	Task Approach Incentives	Increase speed and probability-of-success in translation Bridge gaps in the translational process Translation-Incentives (<i>ToM</i>)
BIH-Innovation	<i>Transfer</i>	Task Approach Incentives	Increase effectivity of innovation transfer Provide structures and support for effective transfer Innovation-Incentives (<i>IoM</i>)

Technology Readiness Levels (circular, iterative)



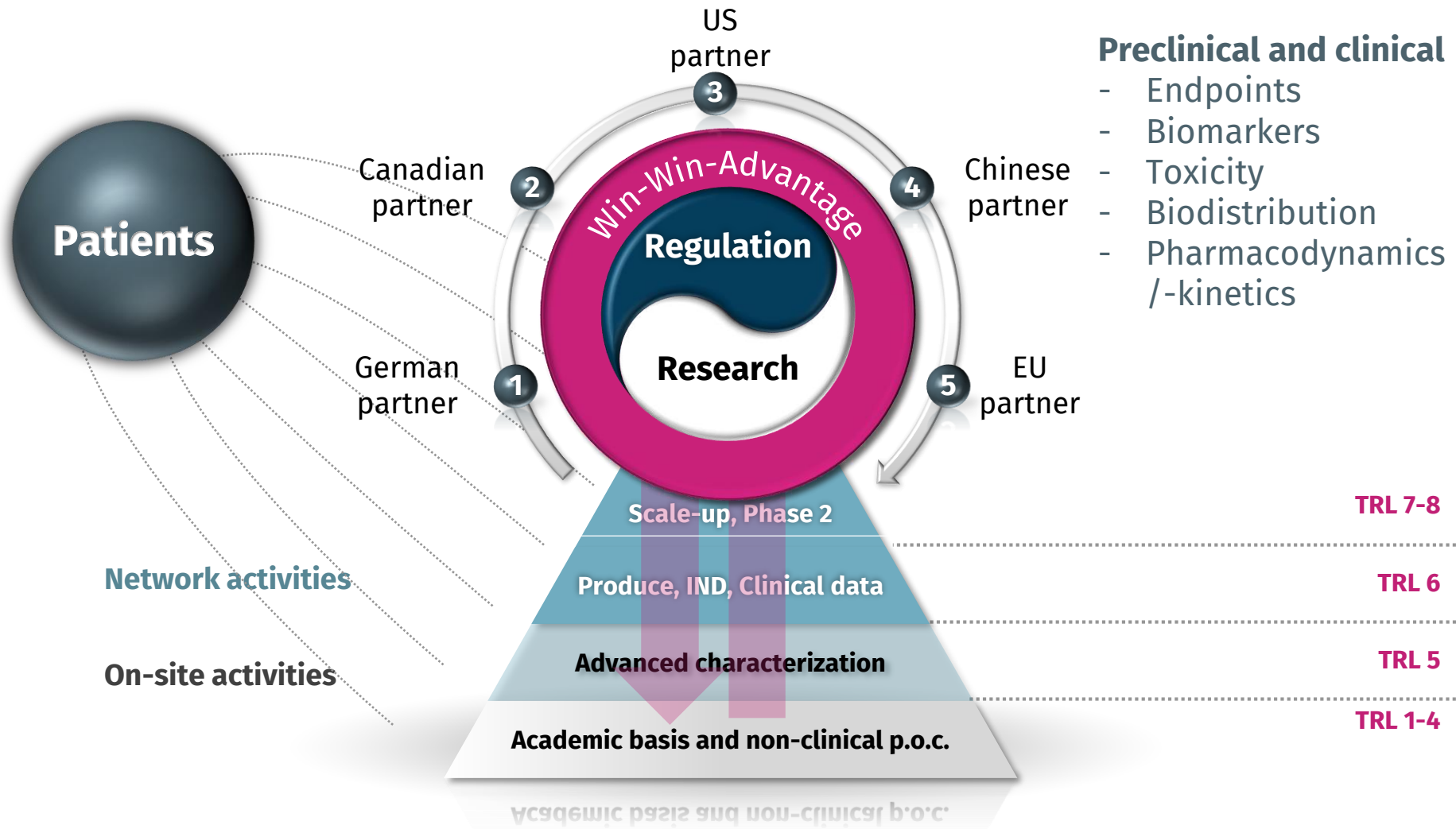
Sideground mindset: Prepared for the unknown

I only know that I know nothing (Socrates) ☹ → ☺

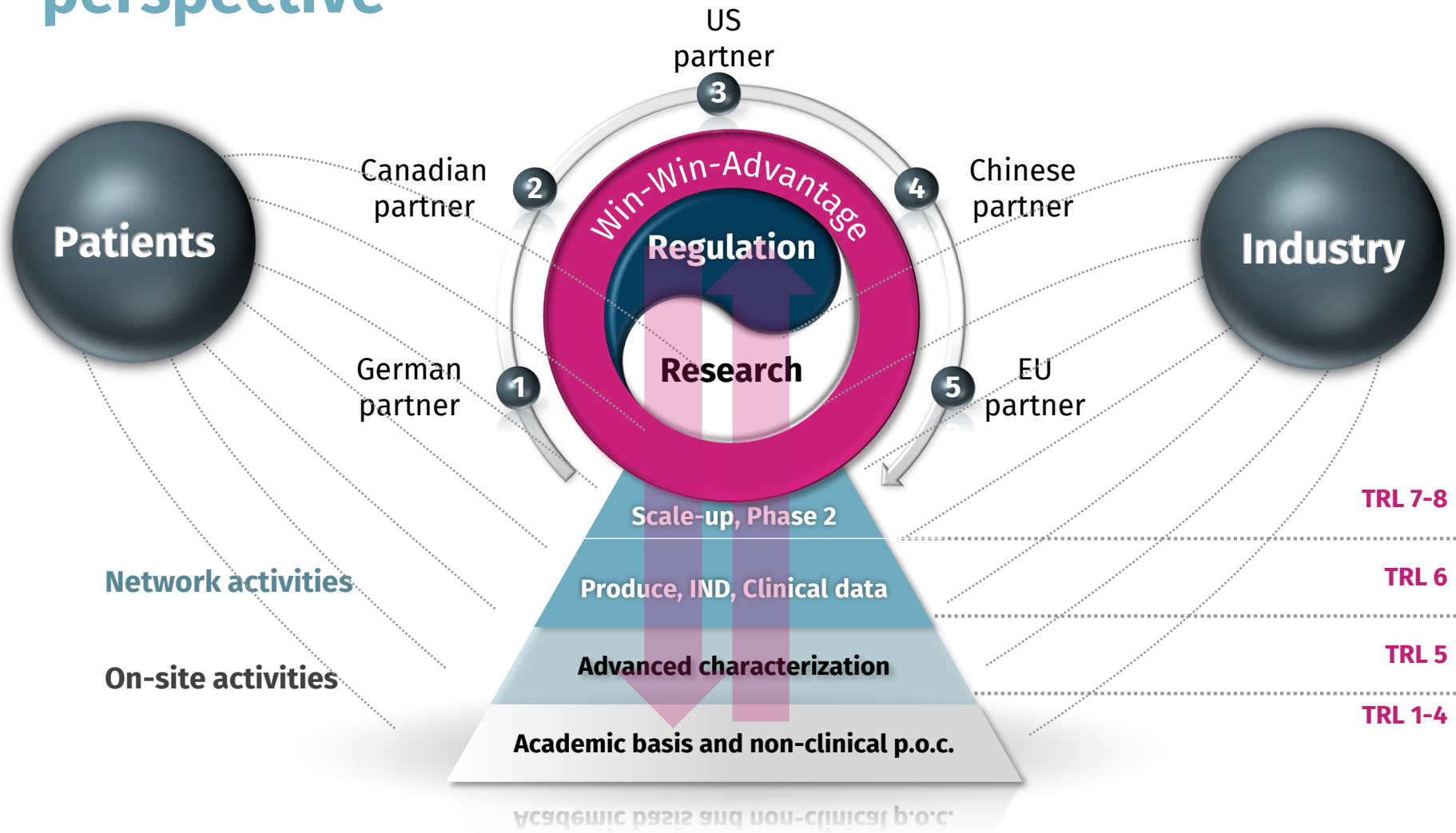
Joni Mitchell: I've looked at clouds from both sides now
From up and down and still somehow
It's clouds illusions I recall
I really don't know clouds at all

The greatest enemy of knowledge is not ignorance,
it is illusion of knowledge (Hawking)

Regulatory and patient perspective



Global team science: includes industry perspective



Positioning of the BIH

ADDITIVE to ROLES of OTHER PLAYERS

University Medicine, DZGs, NUM, Helmholtz,
Fraunhofer, Leibniz, Max-Planck, Industry

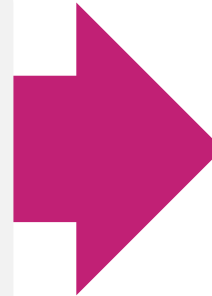
AGILE GOVERNANCE

Finding project-specific regional, national and
international partners

Combine science, business and regulation

MAKING TRANSLATION MEASURABLE

Objective assessment: values and specific project
components



quantitative

precise

reproducible

catalytic

integrative

fair

networking

Governance mindset: Virchow

Zwei Dinge pflegen den Fortschritt der Medizin aufzuhalten:
Autoritäten und Systeme

Two things tend to block progress in medicine: authorities and
systems

BIH to challenge this statement

- Balancing established pathways and new avenues
- Productive, pro-active communication
- Openness to the complexity of challenges
- Institutional governance fostering agility

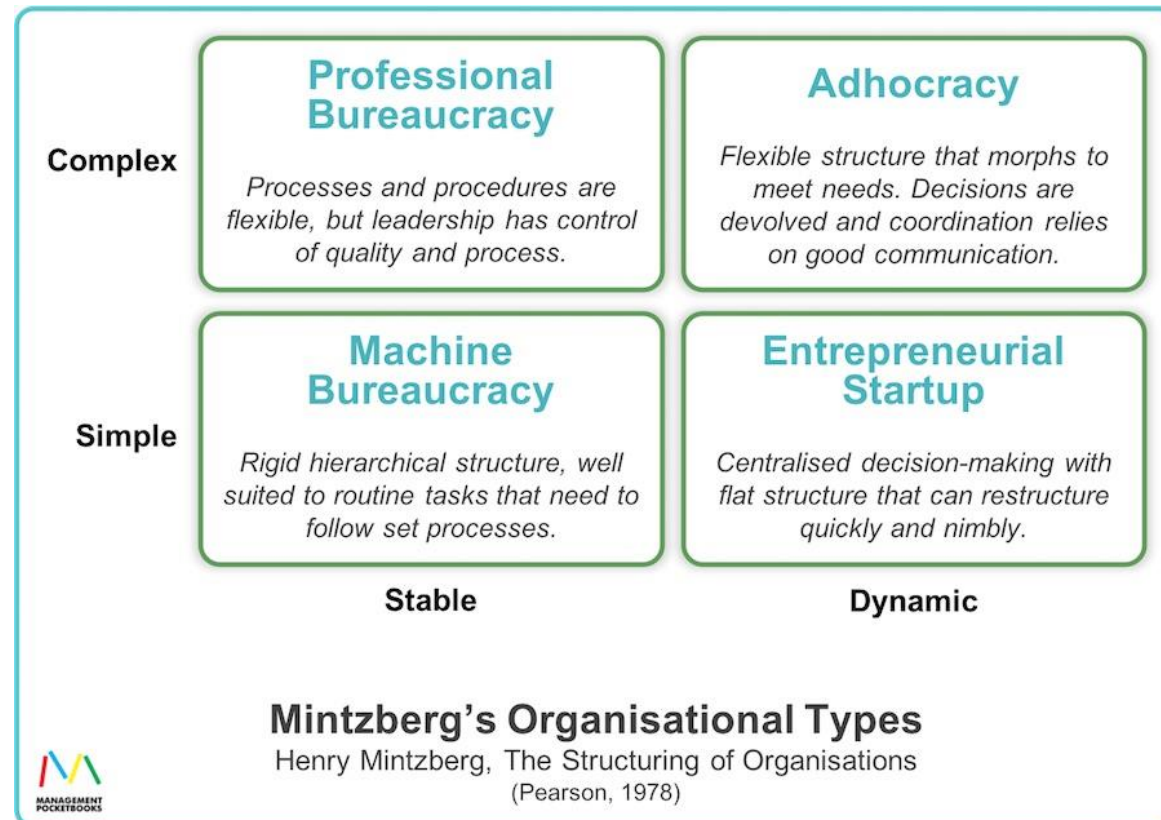


Governance of the BIH



Process-adapted governance

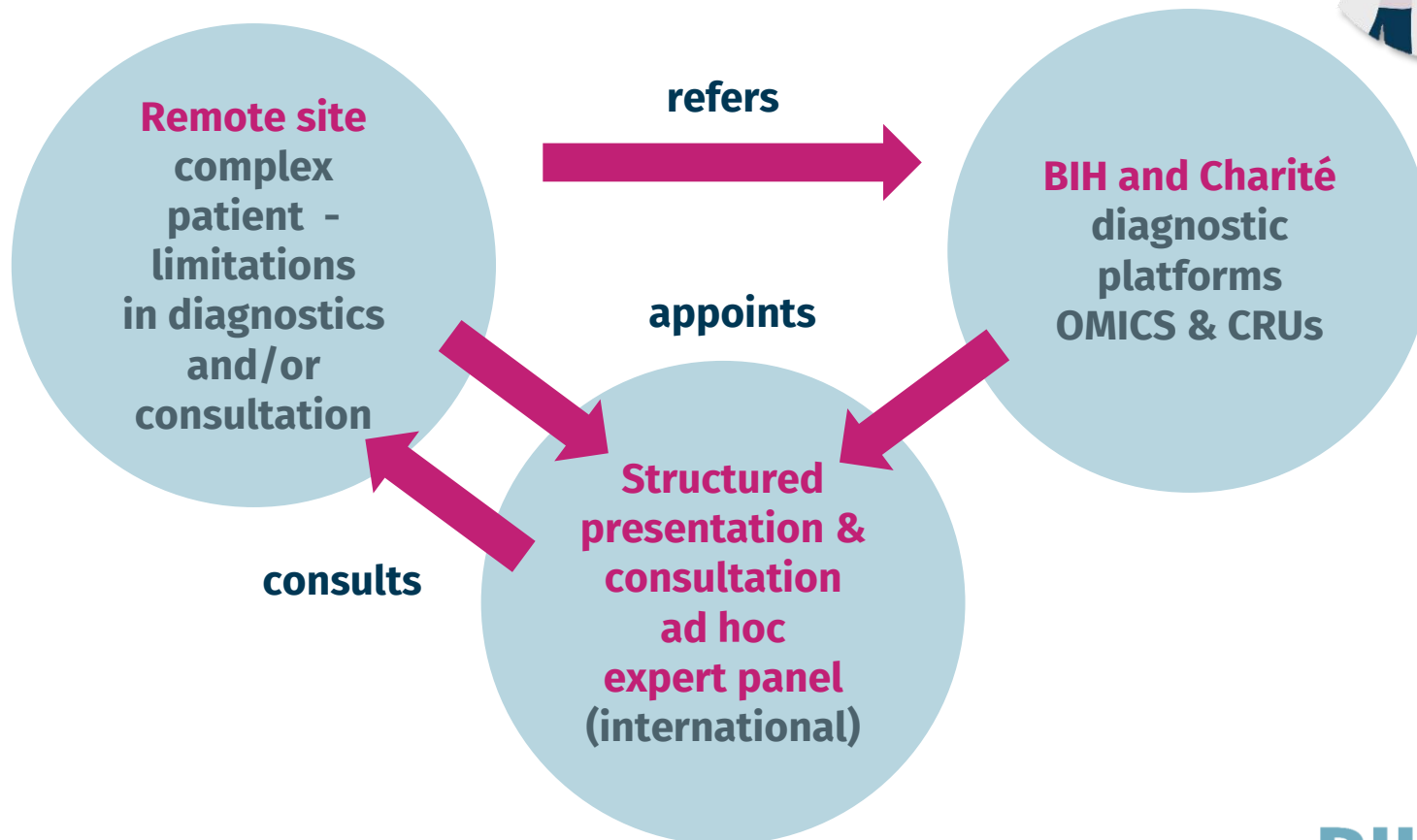
- Professional Organisation
 - Scientific Departments
 - Core Units
 - Academy (BIA) and enabling platforms
- Adhocracy
 - Translational projects
 - Patient consultation



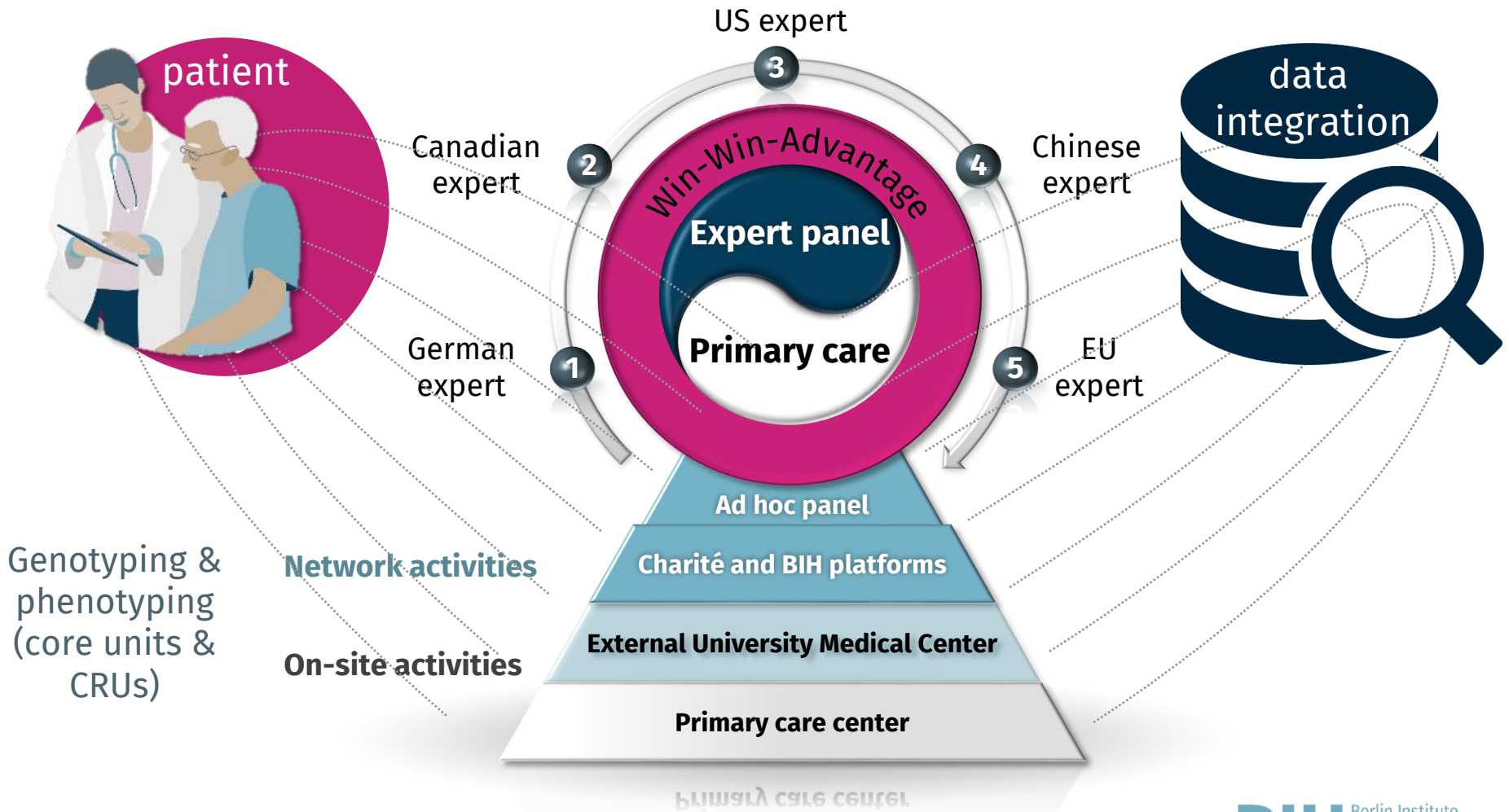
<https://www.pocketbook.co.uk/blog/2018/05/29/adhocracy/>

BIH | Role in patient care

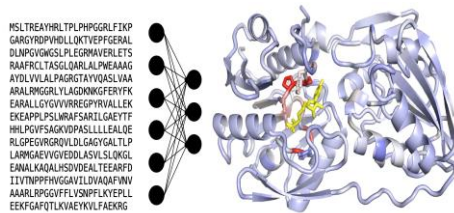
Supportive role for advanced genotyping/phenotyping



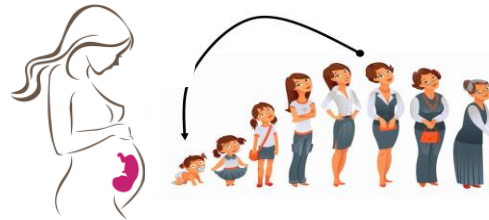
Patient case consultation „adhocracy“



Center for Digital Health



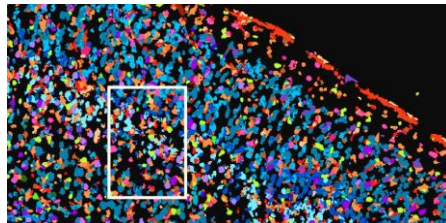
AI in Life Sciences
Roland Eils



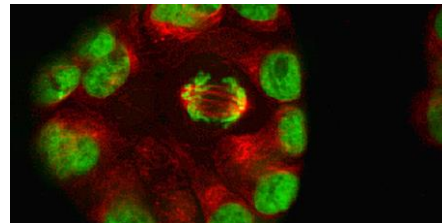
Molecular Epidemiology
Irina Lehmann



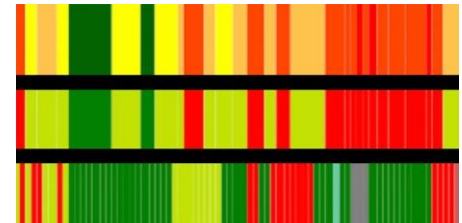
Computational Medicine
Claudia Langenberg



Computational Oncology
Naveed Ishaque



Intelligent Imaging & Genomics
Christian Conrad



Health Data & Cloud
Jürgen Eils & Harald Wagener

Patient eligibility



Third line referral

Patients who are referred by another hospital



Unique care

Patient groups¹ whose DRG products are concentrated for >85% in academic hospitals



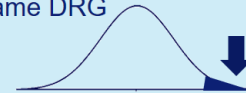
Young multi-morbid

Patients <50 years with 4 or more diagnosis groups in 2 years in all visited hospitals in the country



Treatment intensive

Patients whose treatment was 2 standard deviations more intensive¹ than the one of an average patient in the country with the same DRG



Complicated surgery

Surgeries which are performed for <1:100.000 inhabitants or which are concentrated for >85% in academic hospitals



Multi speciality

Patients for whom three or more specialties³ are involved in treating the same diagnosis



Rare diagnosis

DRG diagnoses for which <1:100.000 inhabitants⁴ receive care in a hospital



Science

Patients with an ICD-10 on which the hospital published many articles and attracts many patients⁵



Erasmus MC
Erasmus

paradigms:
www.dasne.de

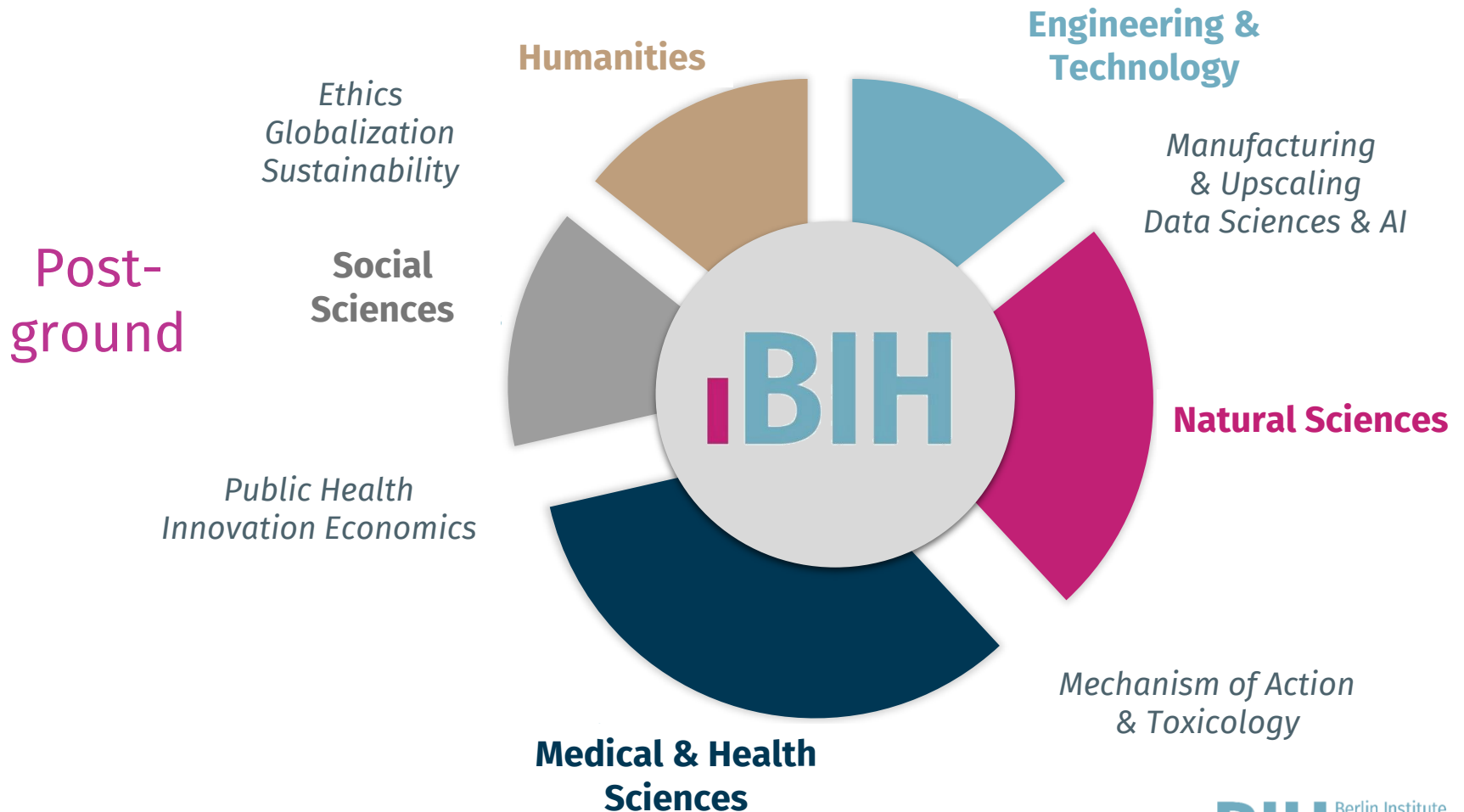
1. Patient groups are created by distinguishing all patients with a certain DRG diagnosis + a gender, DRG diagnosis + an age group, and DRG diagnosis + a travel time category
2. The intensity of a treatment is measured as $\sum(\text{performed procedure} \times \text{average cost of this procedure in all hospitals in the country})$
3. Excluding supporting specialties, e.g. radiology, pathology
4. The definition of the European commission for rare diseases is <1:2000 inhabitants per ICD-10/Orphanetcode. 1<100.000 is used, because the scope of the DRG diagnoses used is broader
5. Minimally 40 publications in 3 years and 50% more patients than expected based on location per ICD-10 chapter (i.e. the first three characters of an ICD-10 code)

Interdisciplinarity of translation

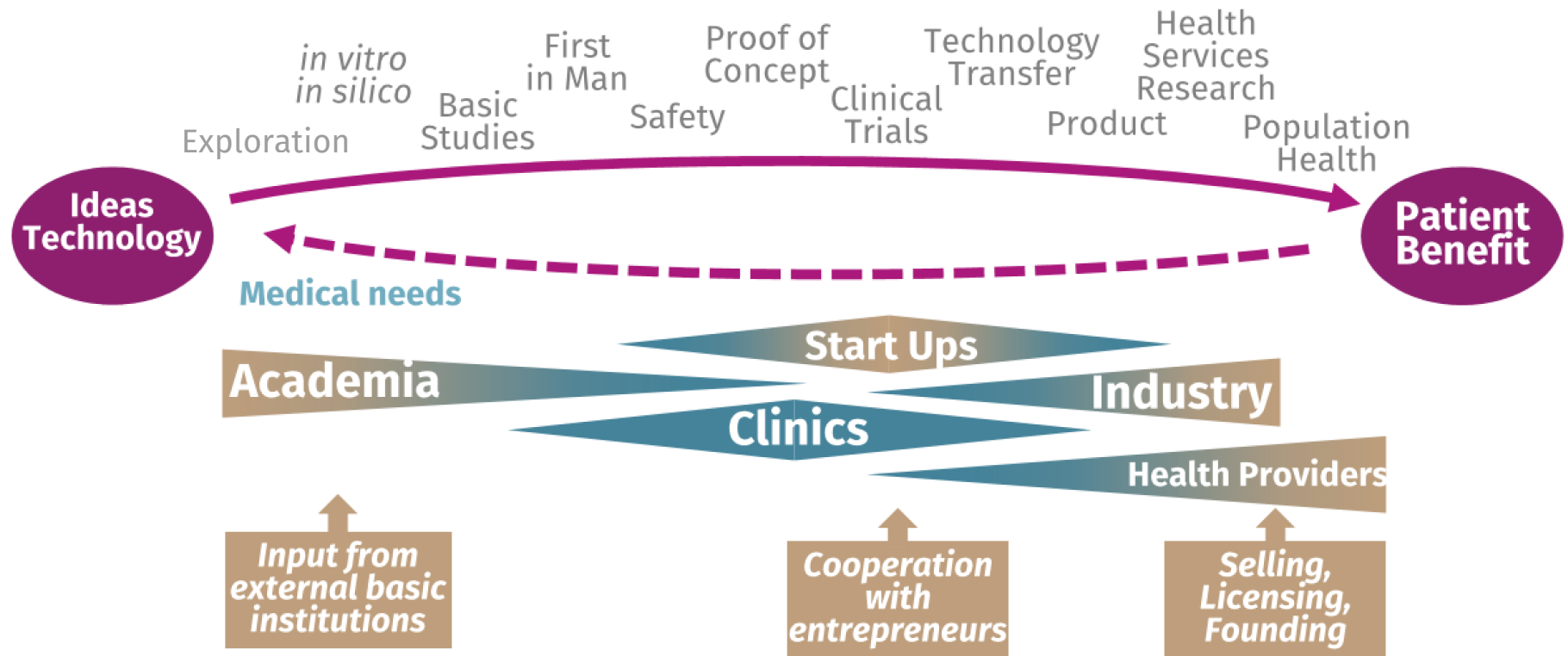
Classification: Fields of Science



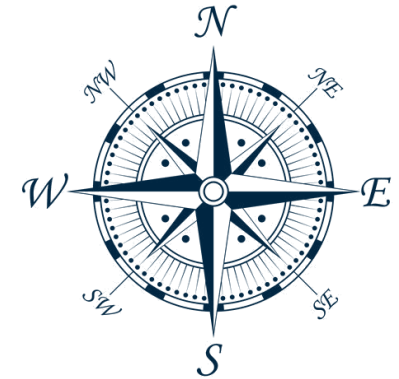
**Berlin University
Alliance**



Berlin ecosystem and partners



Summary



BIH: an institute dedicated to the science of translation
interdisciplinary, precise, objective, reproducible,
catalytic/supportive

Additive to role of other players

Regional, national and international scope

Novel platforms for project assessment/management and patient
case consultation

Focus precision medicine, ATMPs and digital sciences/products

Thank you!

www.bihealth.org



Aus Forschung wird Gesundheit