



Challenges to Mathematical Modelling, Simulation and Data Analysis Arising in Clinical Medicine



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PLAN OF THE REPORT

Challenges in the clinical medicine:

- 1) In Populational research
- 2) In Personalized medicine
- 3) In Basic science research



GLOBAL CHALLENGES IN CLINICAL MEDICINE 2018

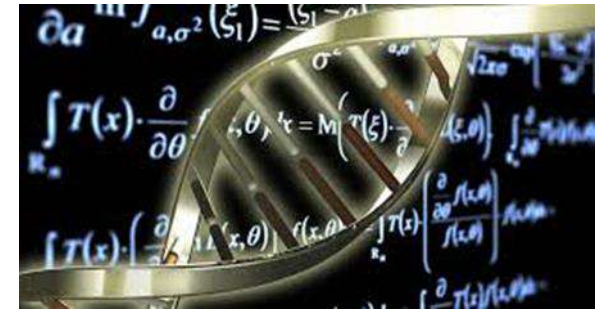
Populational science



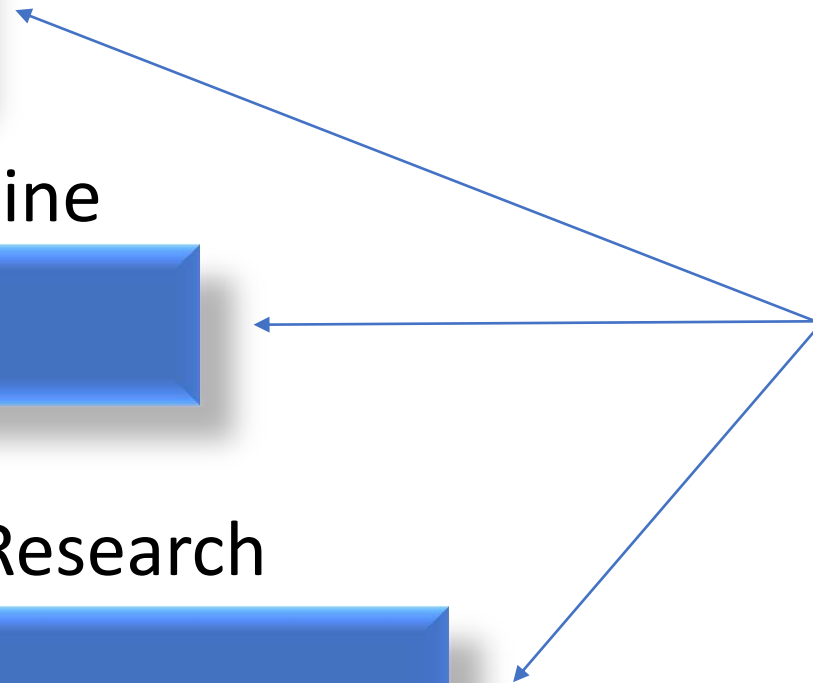
Personalized medicine



Basic Research



Mathematics

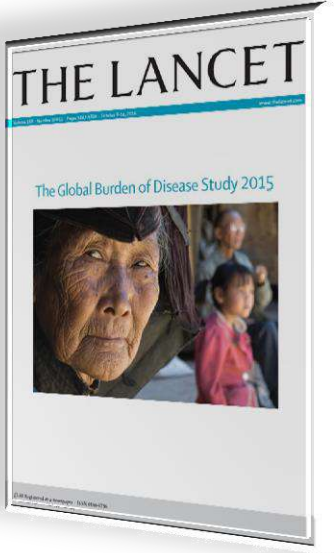


LEVEL ON THE TOP: Populational Research



- Diseases and risk factors research. Global Burden of Disease Study in the world, Russia and other countries. Pilot region to conduct global study on "big data" in epidemiology
- Medical-informational center in Russia and Bashkortostan

WHAT IS GLOBAL BURDEN OF DISEASES STUDY (GBD)?



The Global Burden of Disease (GBD) is a systematic, scientific effort to quantify the comparative magnitude of health loss due to diseases, injuries, and risk factors by age, sex, and geographies for specific points in time.

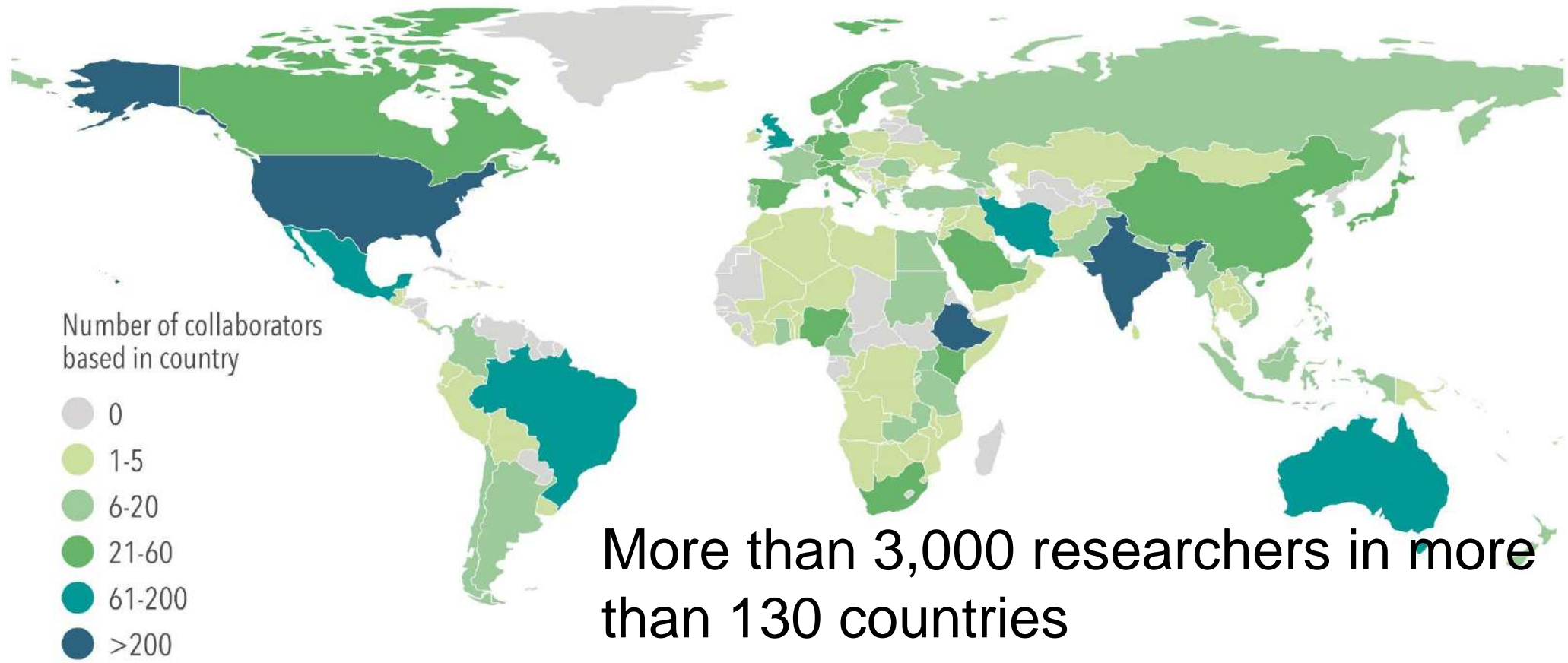
About GBD | Institute for Health Metrics and Evaluation.
(2018). Healthdata.org. Retrieved 13 June 2018, from
<http://www.healthdata.org/gbd/about>



FOCUS ON ALL ASPECTS OF HEALTH

- Mortality
- Incidence, prevalence
- Years of life lost (YLLs) to premature death
- Years lived with disability (YLDs)
 - Time spent sick or injured
- Disability adjusted life years (DALYs)
 - Years of healthy life lost

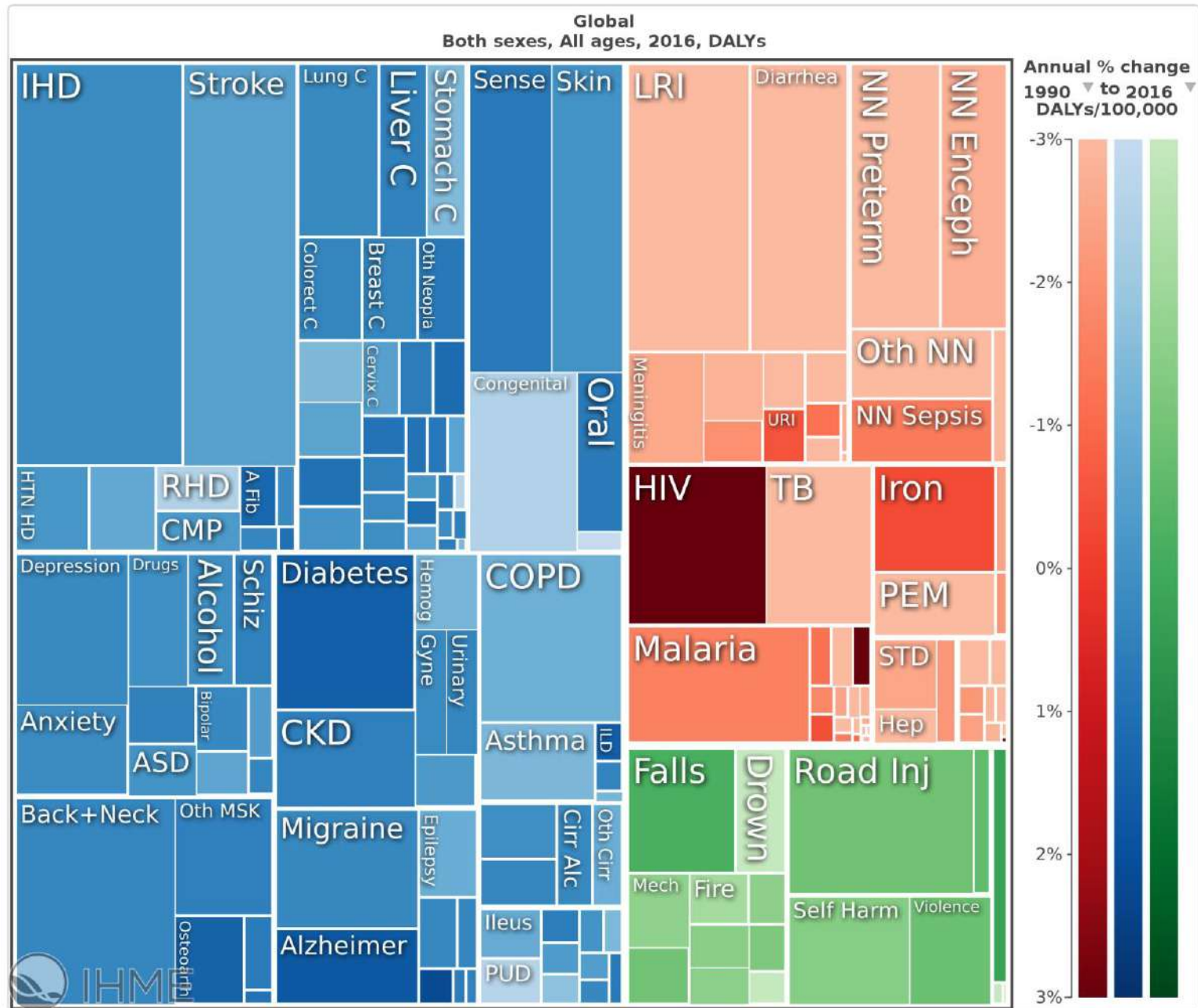
DATA COLLECTED GLOBALLY



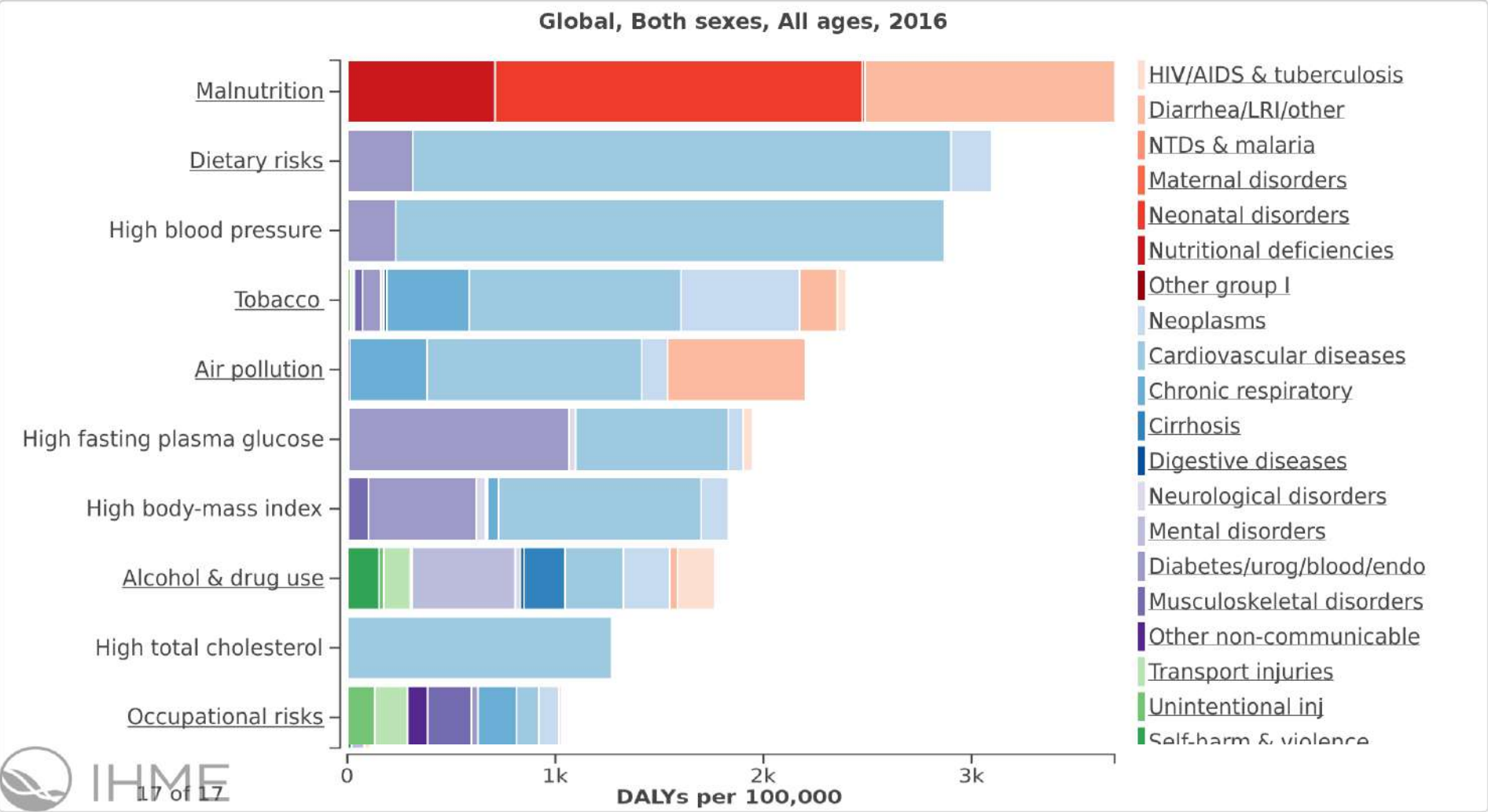
GLOBAL: DALY

DALY stands for disability-adjusted life years.

Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2017. Available from <http://vizhub.healthdata.org/gbd-compare>.



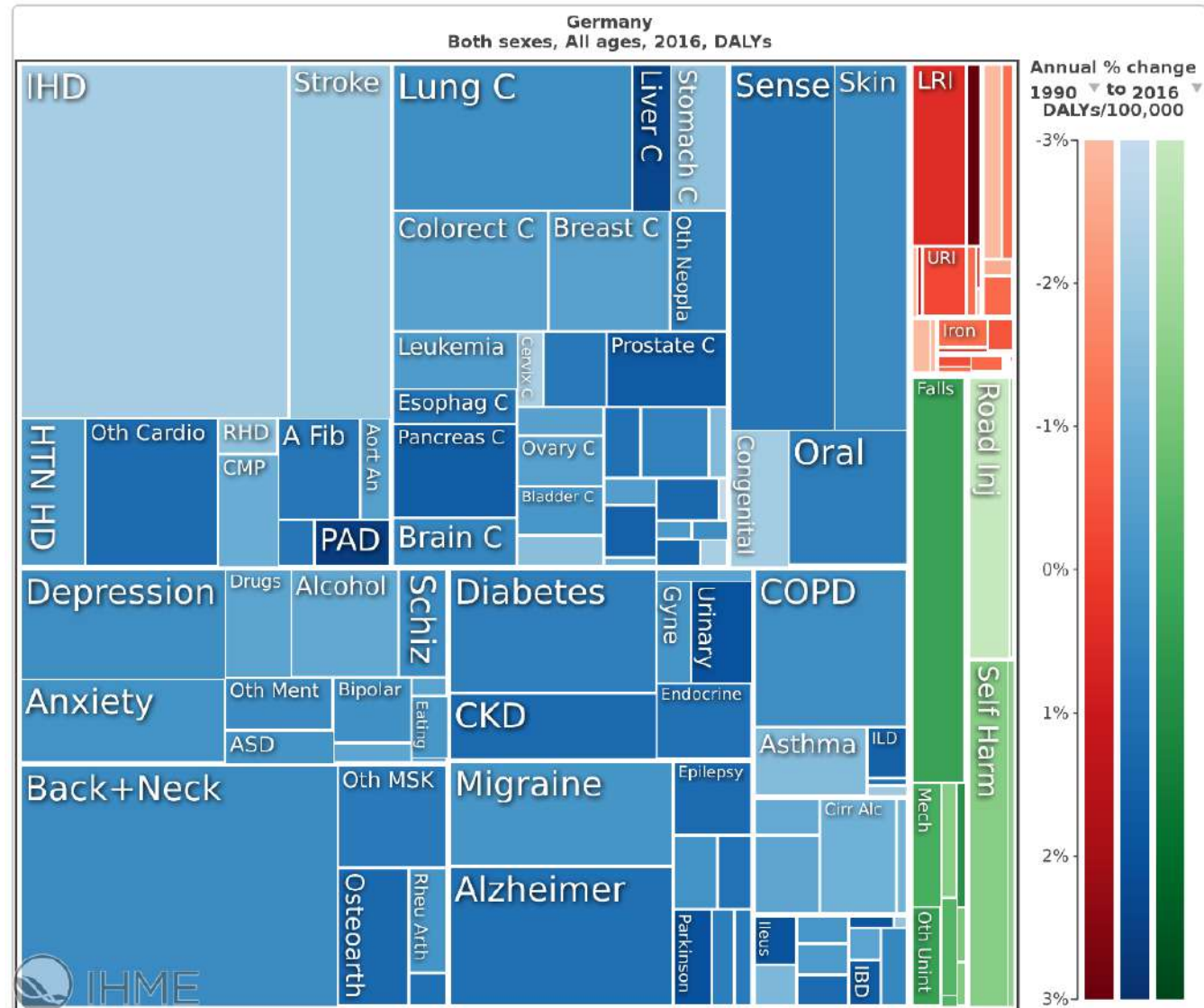
GLOBAL: RISK FACTORS



COMPARE TO GERMANY

DALY stands for disability-adjusted life years.

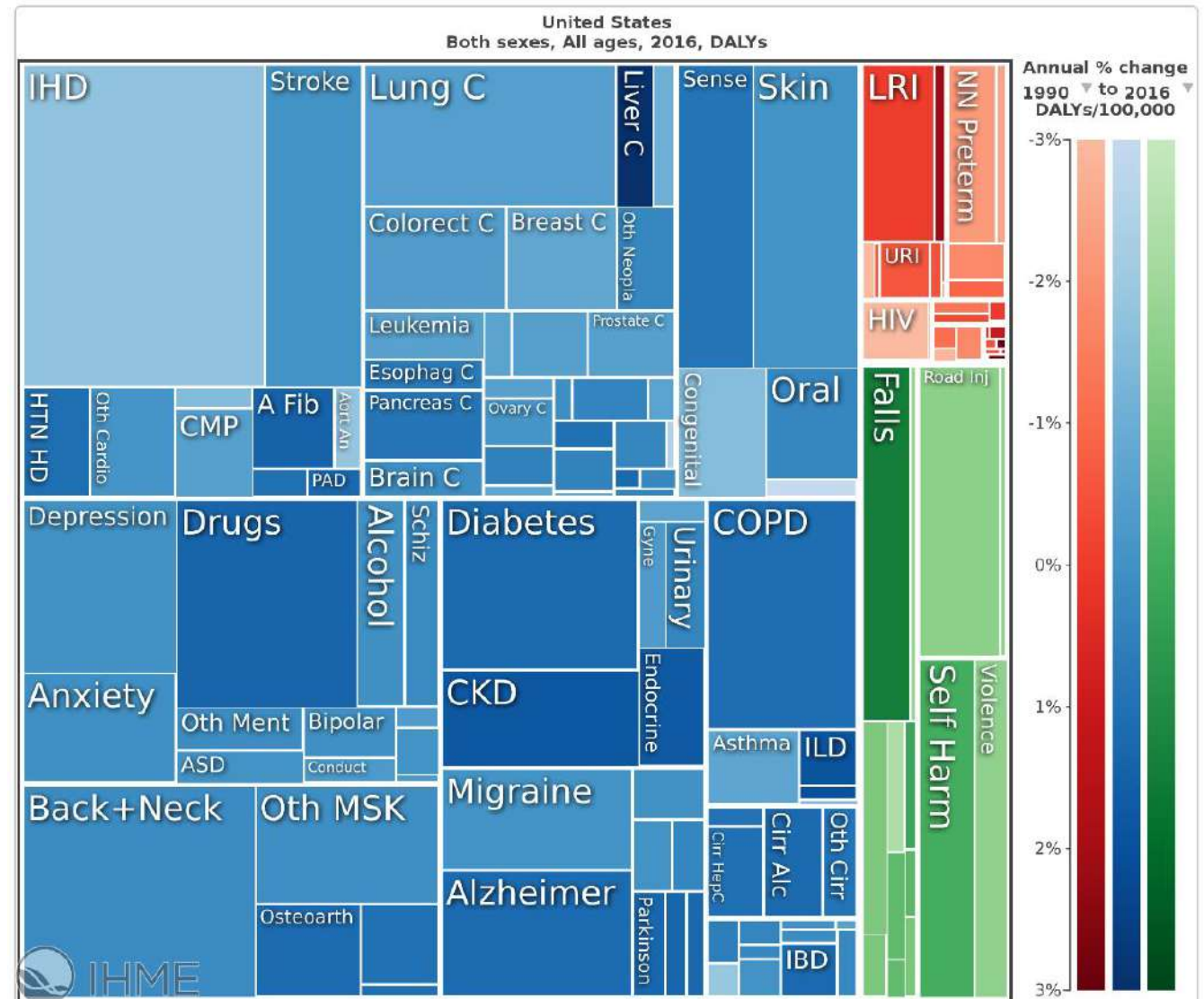
Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2017. Available from <http://vizhub.healthdata.org/gbd-compare>.



COMPARE TO USA

DALY stands for disability-adjusted life years.

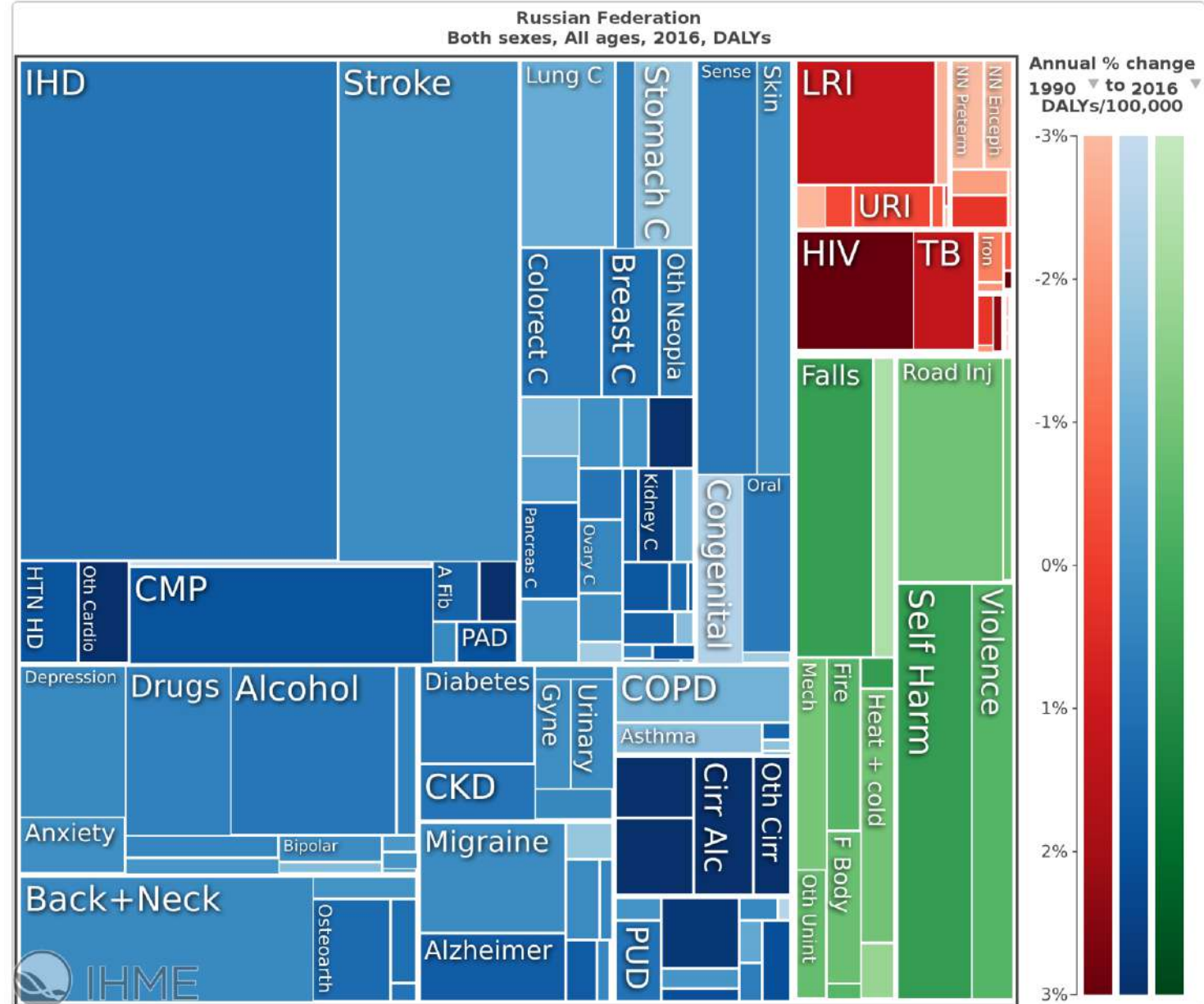
Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2017. Available from <http://vizhub.healthdata.org/gbd-compare>.



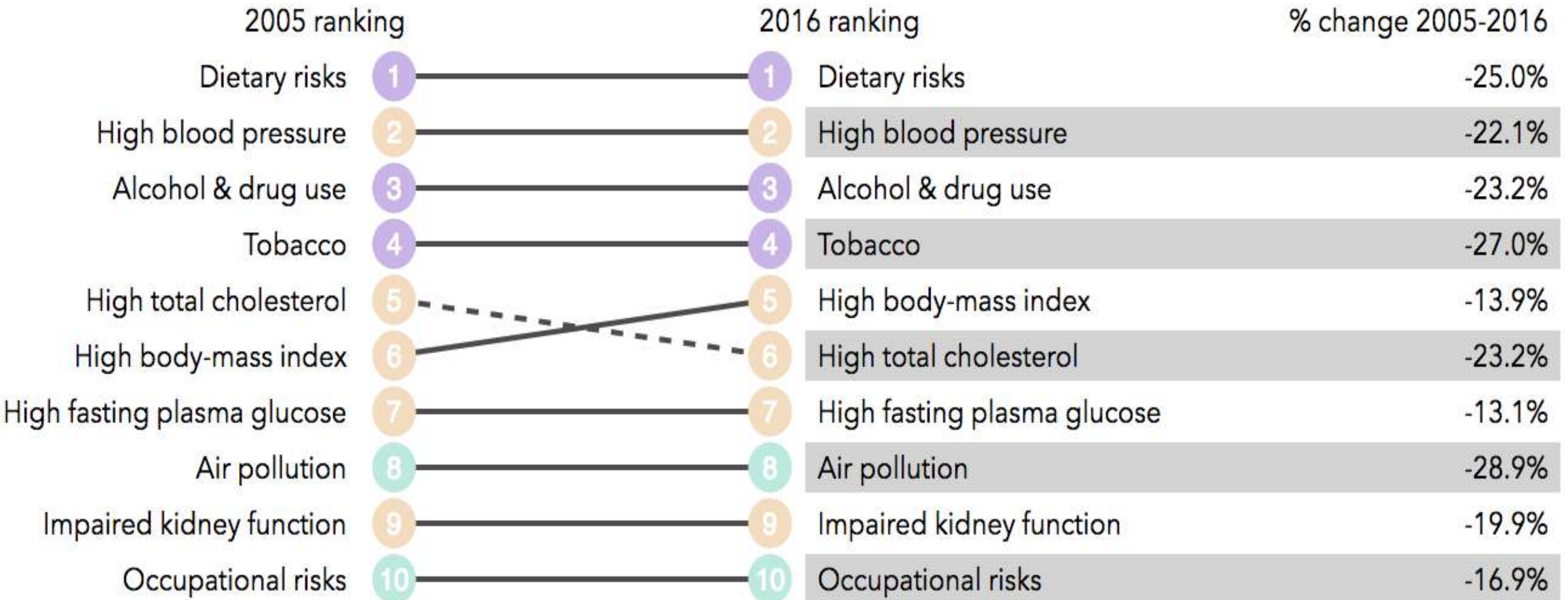
COMPARE TO RUSSIA

DALY stands for disability-adjusted life years.

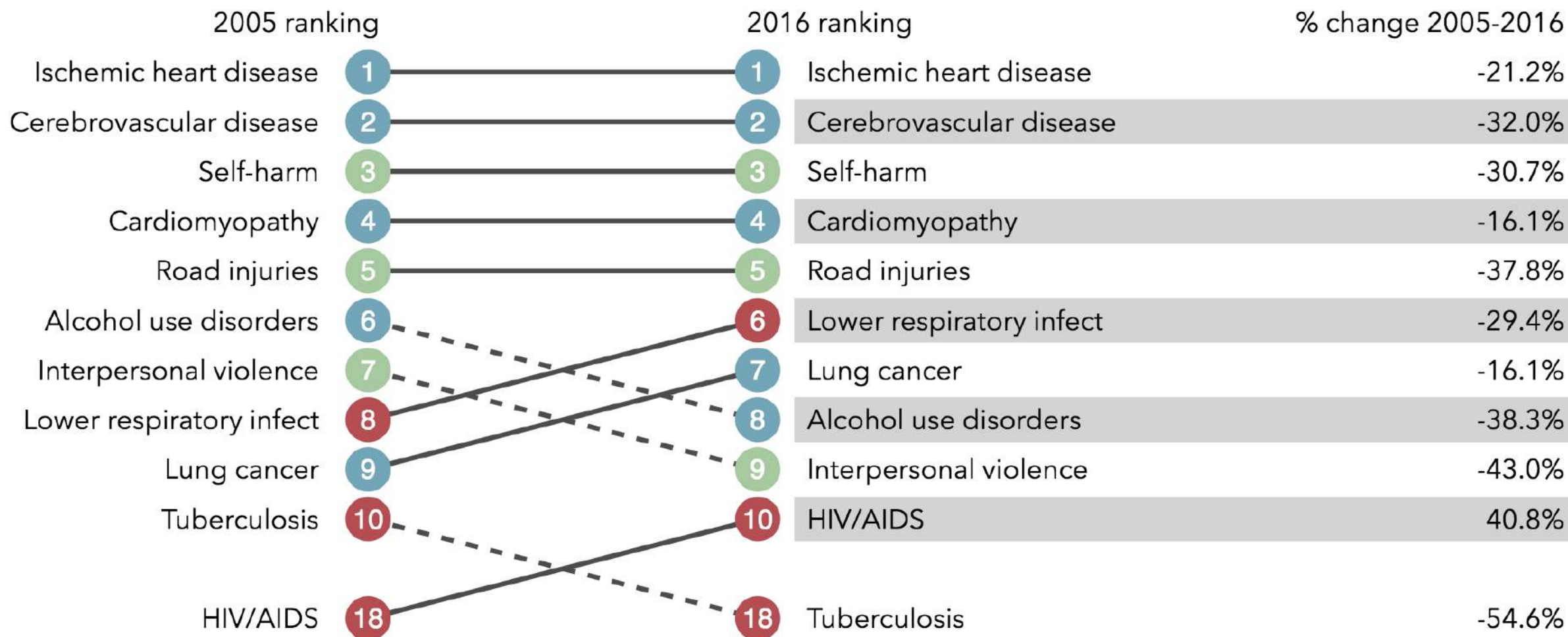
Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2017. Available from <http://vizhub.healthdata.org/gbd-compare>.



RUSSIA: RISK FACTORS



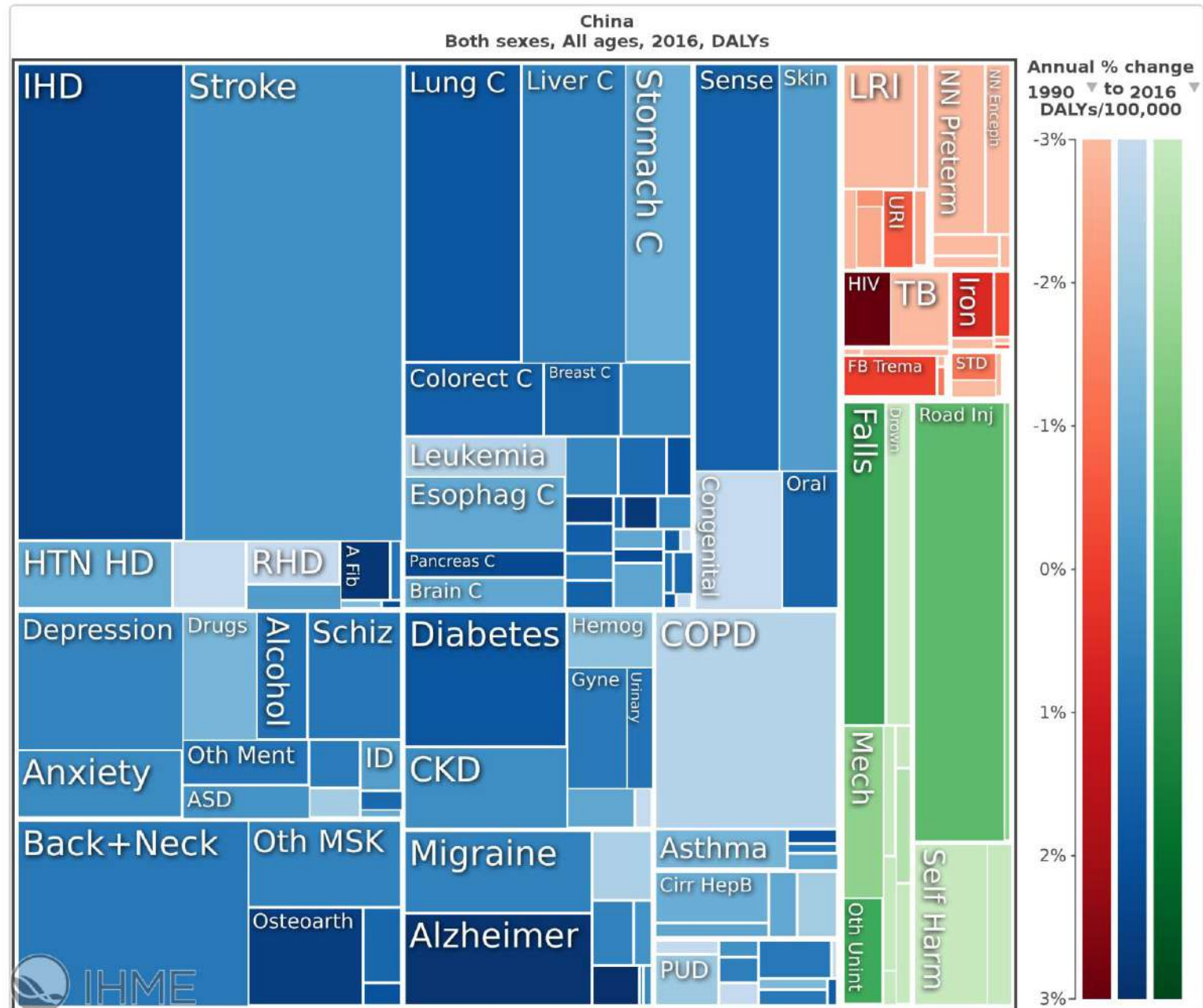
RUSSIA:PREMATURE DEATH



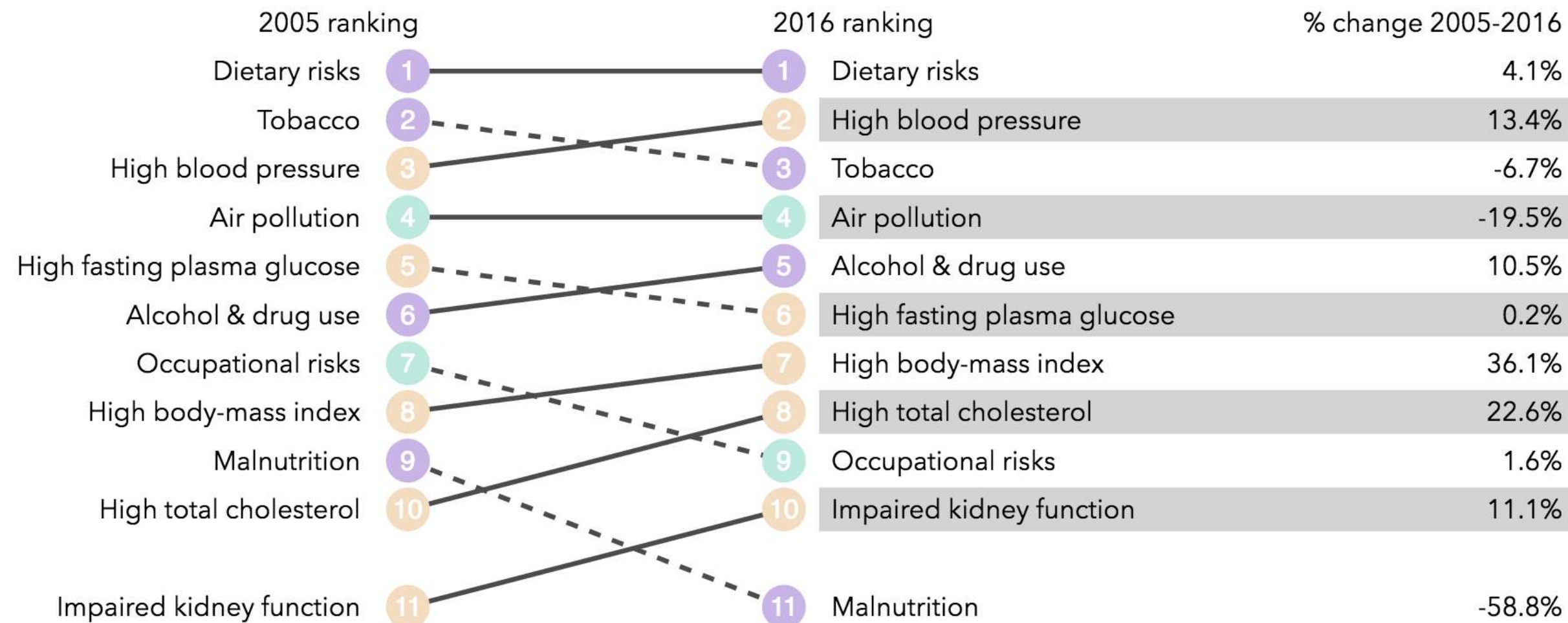
COMPARE TO CHINA

DALY stands for disability-adjusted life years.

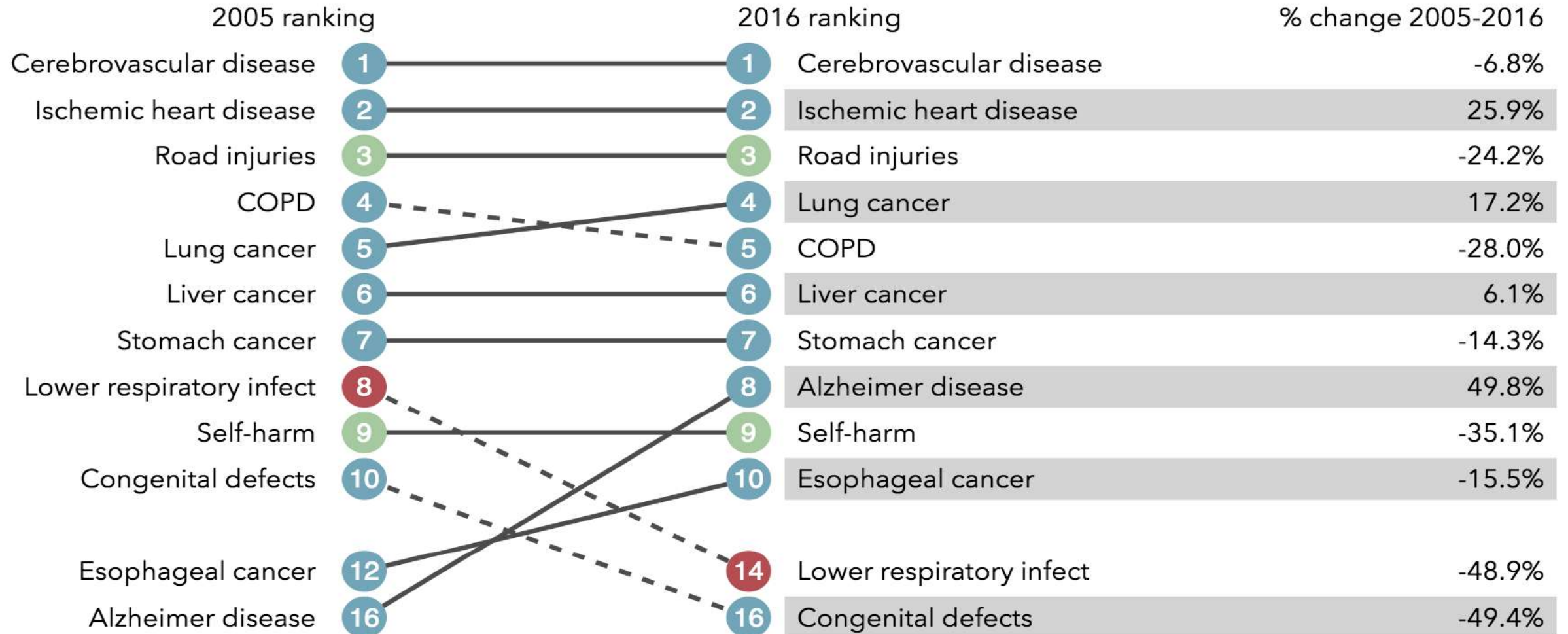
Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2017. Available from <http://vizhub.healthdata.org/gbd-compare>.



CHINA: RISK FACTORS



CHINA: PREMATURE DEATH (YLL)



REPUBLIC BASHKORTOSTAN



The capital – the city of **UFA**



The population of the region is **4,1 mln people**



The total area is **143 000 sq. km.**

The Republic ranks **7th** in population in Russia
The density of population is – **28,3** people per 1 square kilometer against average **8,3** people in Russia

Gross regional product



20,8
bln \$

Industrial output

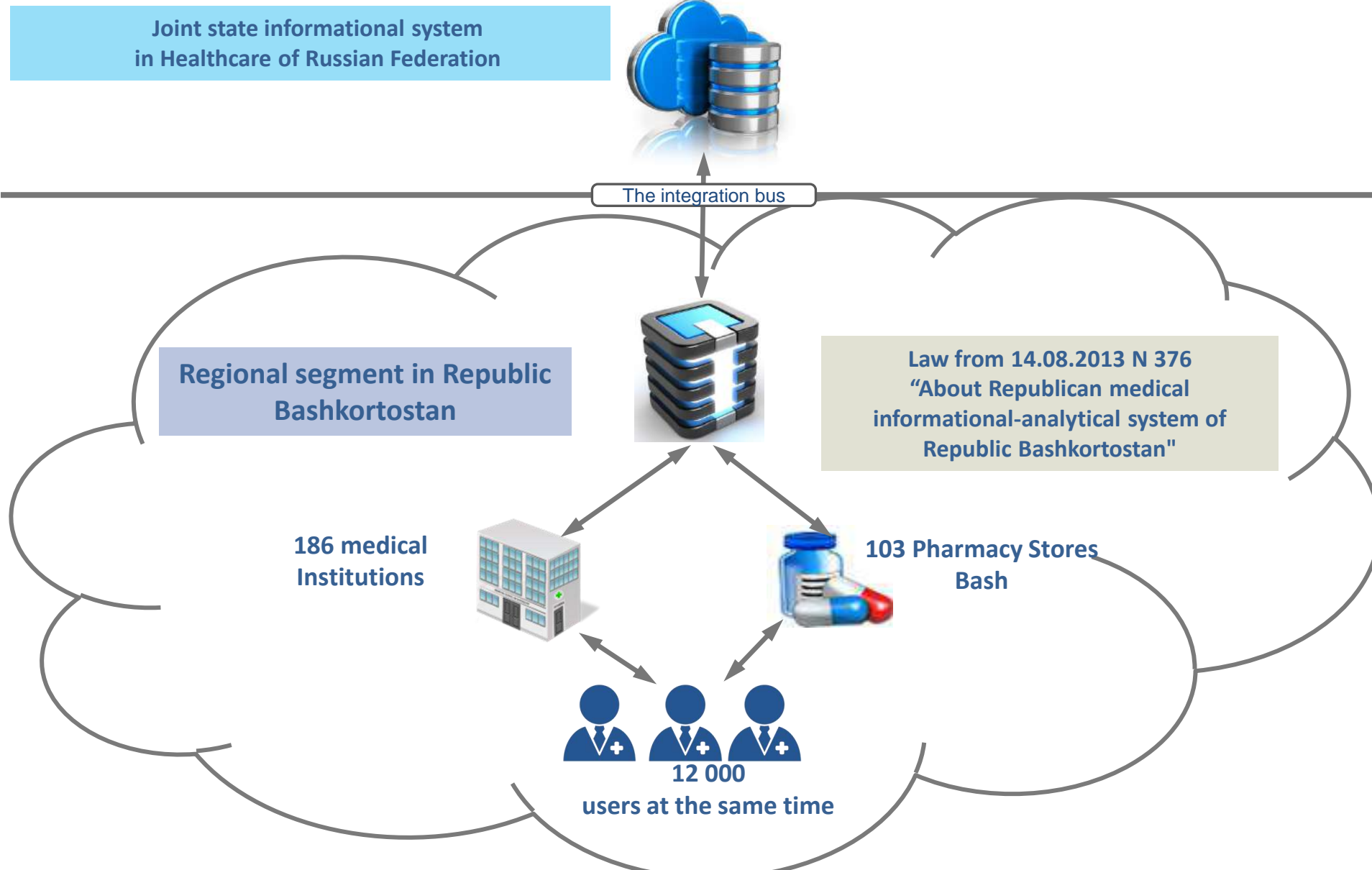


Ranks 9th
in gross regional
product in Russia



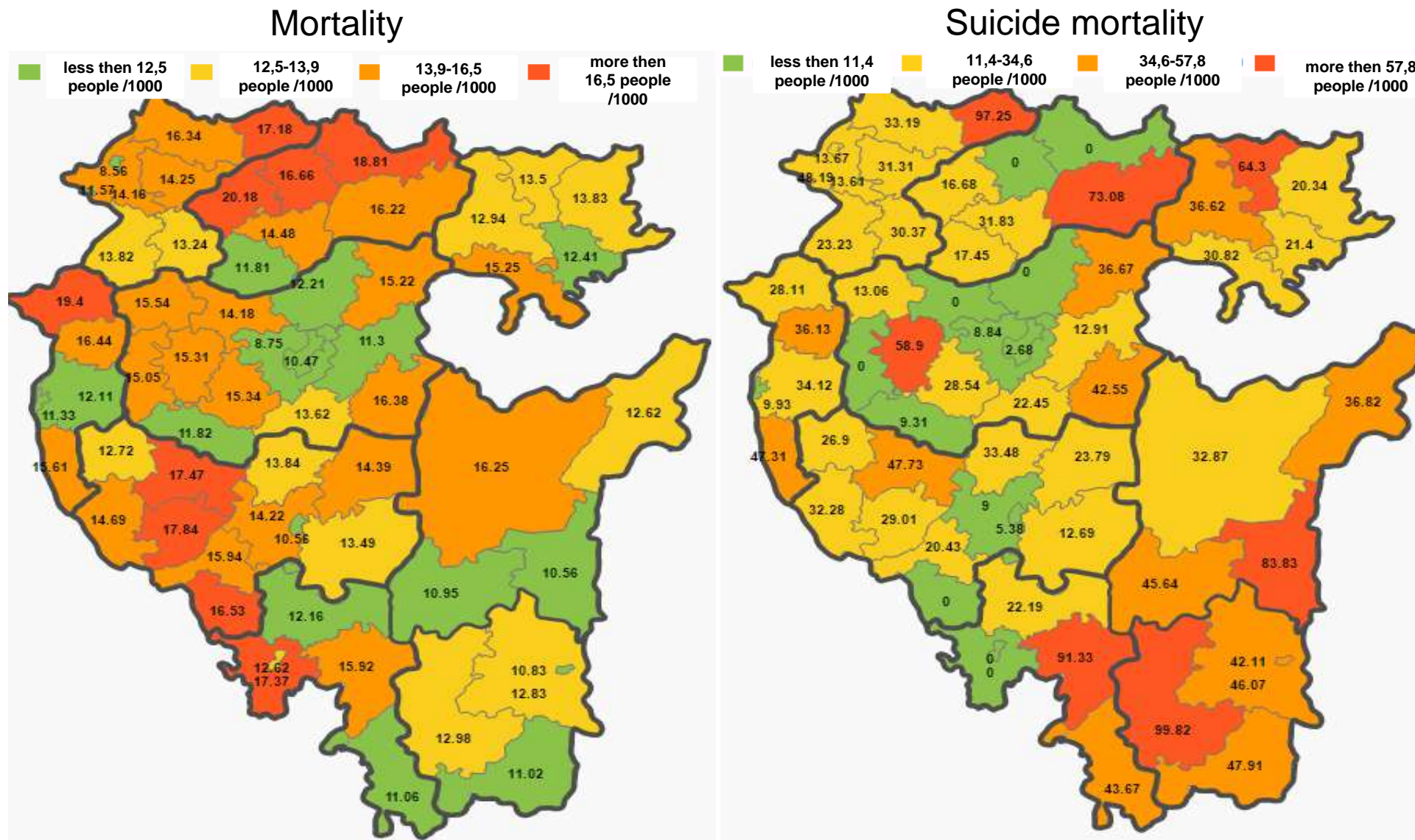
In Republic:
15000 physicians
45000 nurses

REPUBLICAN MEDICAL INFORMATIONAL-ANALYTICAL SYSTEM IN REPUBLIC BASHKORTOSTAN



CENTER FOR SITUATION AND PROJECT DECISION OF BASHKORTOSTAN REPUBLIC

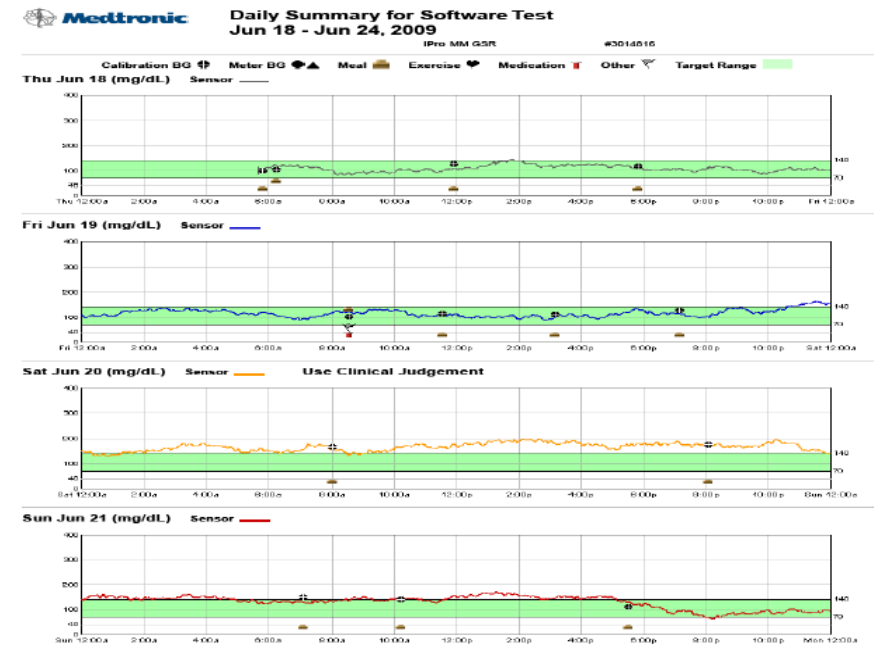
MORTALITY IN REGION



INTERREGIONAL CENTER OF INSULIN PUMPS OF BSMU CLINIC



- ✓ Experience with pumps 4 generations.
- ✓ Installed and used more than 300 insulin pumps with a good result.



- ✓ Round-the-clock remote monitoring of glucose with data output in electronic and printed form.

WHY MEDICAL STANDARDS DO NOT FUNCTION IN 100 % OF CASES ?

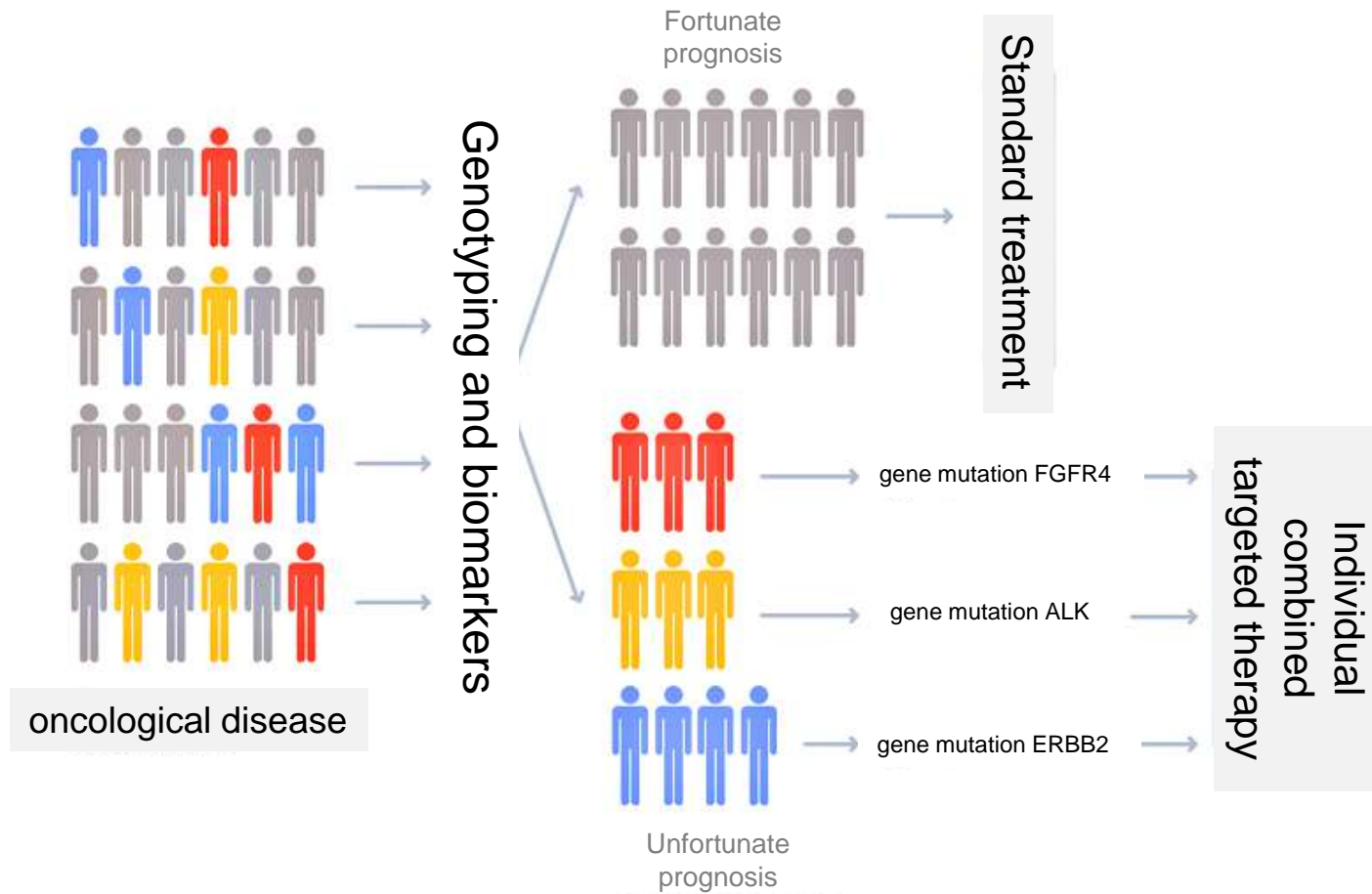


Evidence based medicine on clinical trials and population studies

Evidence based medicines in special monogenous cohorts

Personalized medicine

PERSONALIZED TREATMENT (AT THE EXAMPLE OF COLORECTAL CANCER)



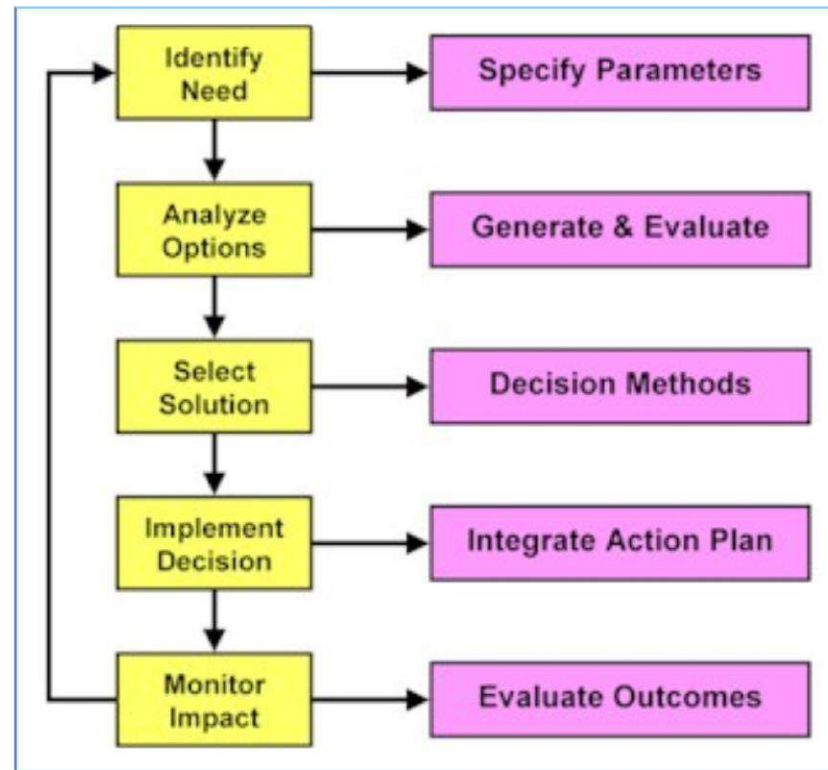
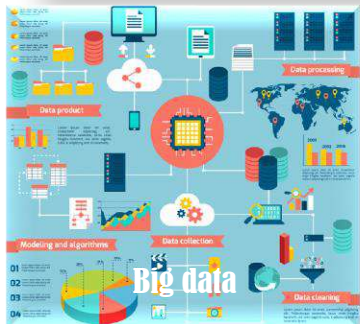


STEP DOWN:

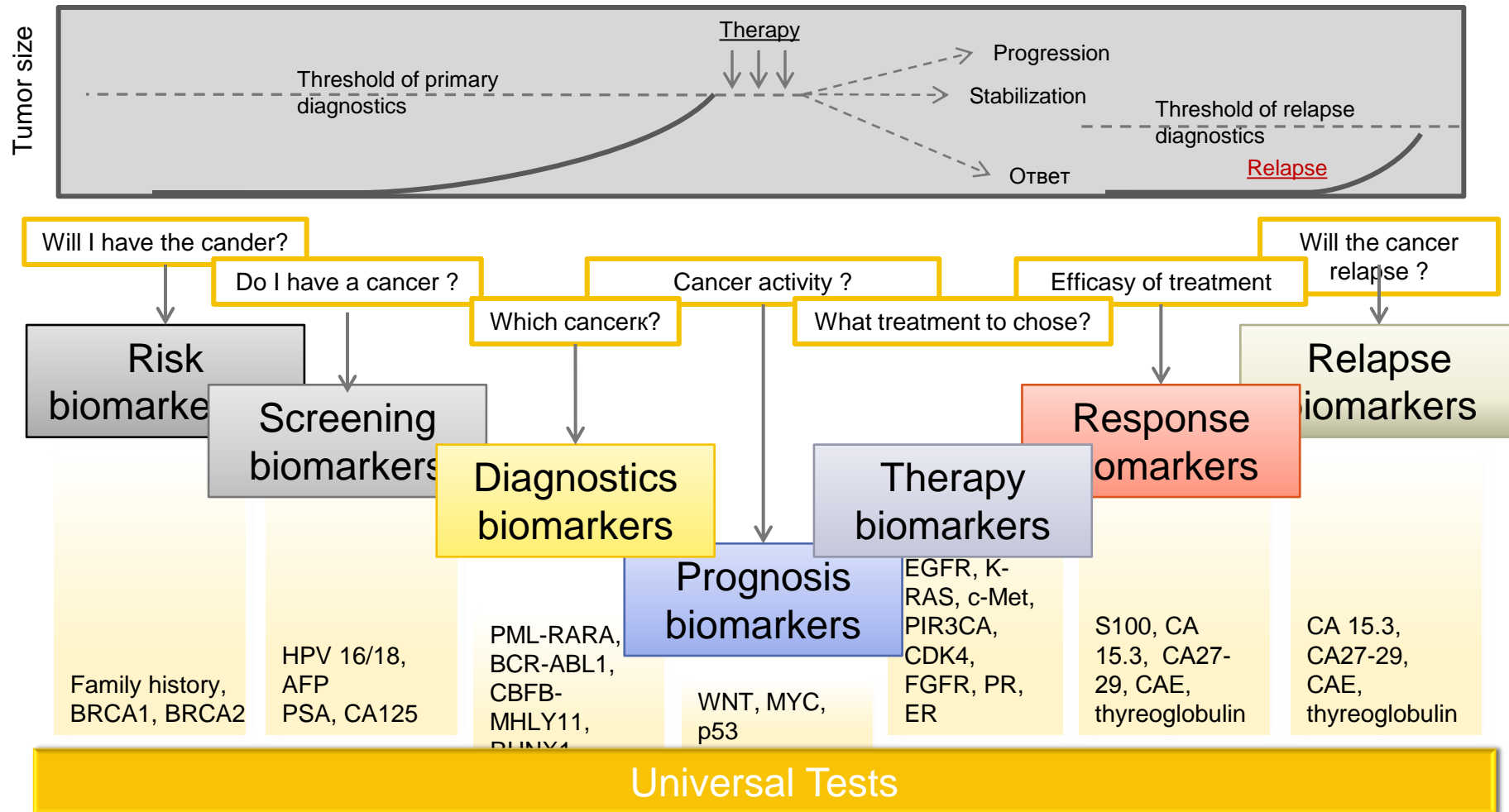
CHALLENGE IN PERSONALIZED MEDICINE DATA ANALYSIS

- ✓ **Biomarker analysis**
- ✓ **Digital therapeutics**
- ✓ **Genetics**

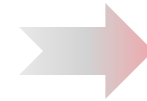
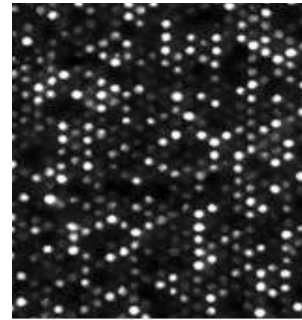
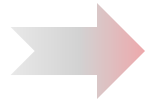
DRUG ADMINISTRATION DECISION-MAKING SYSTEMS



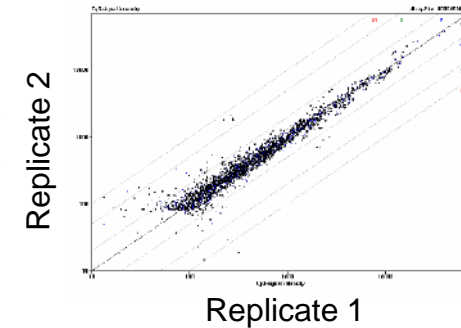
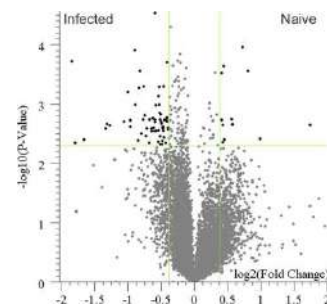
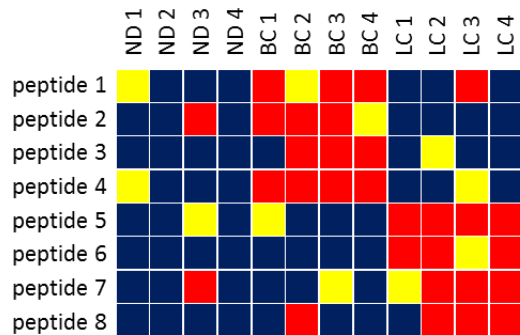
BIOMARKERS SCREENING AS ONE OF THE BASES OF PERSONALIZED MEDICINE



MULTIMARKER ANALYSE



Peptide	Intensity	Abundance	Retention Time	Mass	Charge	Sequence
1	1000	500	1.2	1000	2	AGK
2	2000	1000	1.5	1200	3	AGK
3	3000	1500	1.8	1400	4	AGK
4	4000	2000	2.1	1600	5	AGK
5	5000	2500	2.4	1800	6	AGK
6	6000	3000	2.7	2000	7	AGK
7	7000	3500	3.0	2200	8	AGK
8	8000	4000	3.3	2400	9	AGK
9	9000	4500	3.6	2600	10	AGK
10	10000	5000	3.9	2800	11	AGK



WHAT IS DIGITAL THERAPEUTICS?

Panacea Cloud is a first in Russia Digital Therapeutic solution.

Digital therapeutics, is a health discipline and treatment option that utilizes a digital and often online health technologies to treat a medical condition.

Could be scalable and cost effective yet not enough evidence.



PANACEA CLOUD

First Digital Therapeutic Solution in Russia and developed in Bashkortostan

RBTODAY

Булат Идрисов: Мы не хотим зарабатывать на болезнях людей, цель – достичь благоприятного результата

Роман Якимчук - 29/07/2018



Минздрав заинтересован в блокчейн-проекте ученых из Башкирии

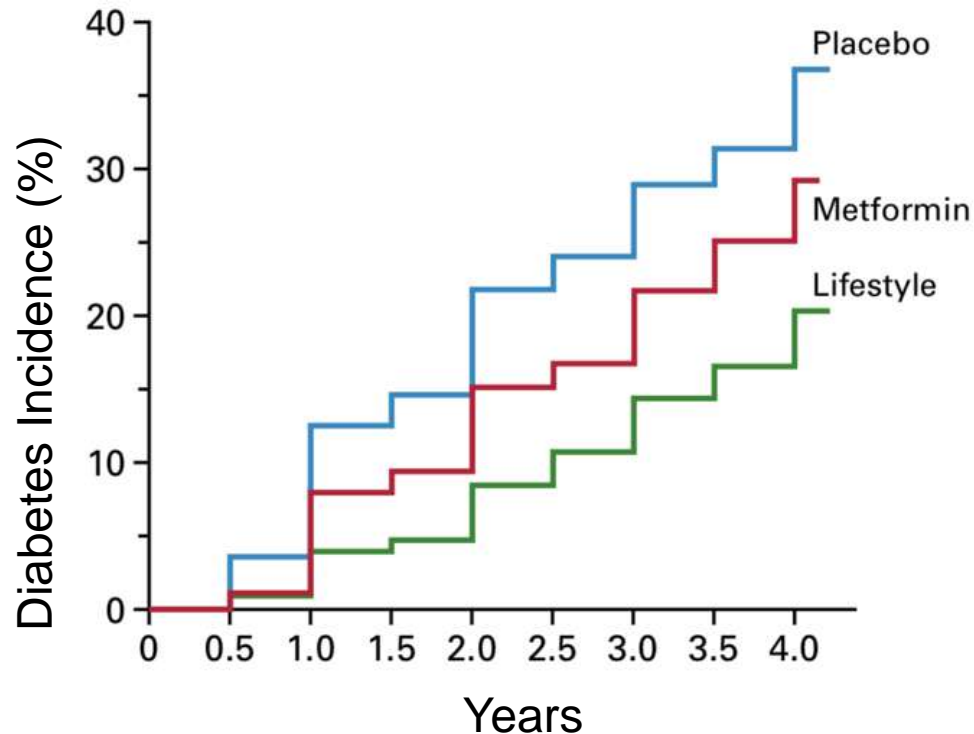
Основатели «Panacea.Cloud» обсудили с экспертами из Министерства здравоохранения, Росздрава и других госучреждений возможности внедрения медицинских информационных систем на основе



«Клиника в облаке» авторов из Башкирии победила в хакатоне в Петербурге

«Система похожа на большую библиотеку, где на каждую болезнь написан свой алгоритм»

METABOLIC SYNDROME TREATMENT



Diabetes Prevention Program Research Group. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England journal of medicine*, 346(6), 393-403.

- Effectiveness of the curriculum was established in RCTs
- Later the digital analog of the curriculum in the USA was shown to be as effective as the original
- Panacea Cloud is a pioneer of digital therapeutics in Russian speaking world and currently undergoing pilot tastings

HOW PANACEA.CLOUD WORKS?

Online guide that helps to form healthy habits on nutrition, physical activity and mental health via

- Smartphone
- Case management
- Disease Control Prevention Program
- Just in time adaptive intervention
- Tokens to stimulate health behaviors

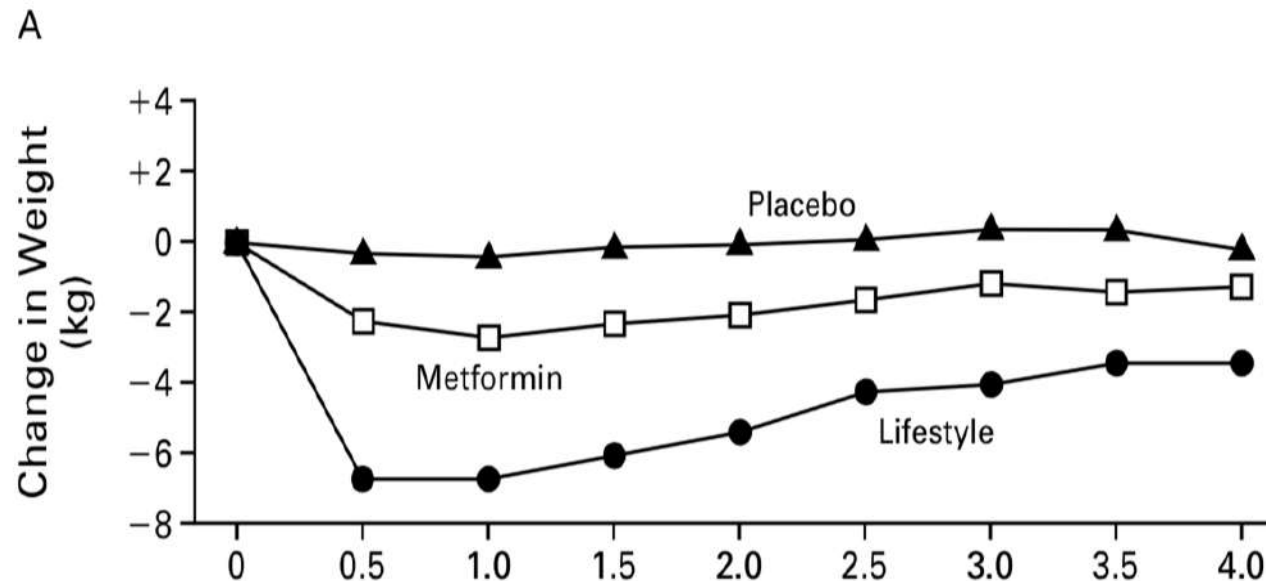




PANACE.CLOUD: ADVANTAGE

Evidence-Based Curriculum of CDC Diabetes Prevention standards.

Clinical effectiveness demonstrated in clinical trials

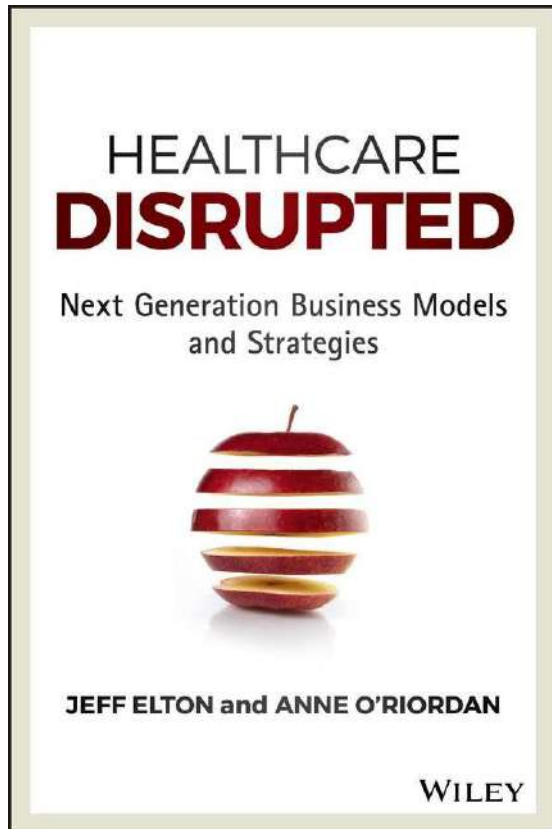


PANACEA CLOUD PROTOTYPE

Chat bot prototype video link <https://youtu.be/plCeZLmqigQ>

Case managers interface prototype <https://youtu.be/vetfU6tLLik>



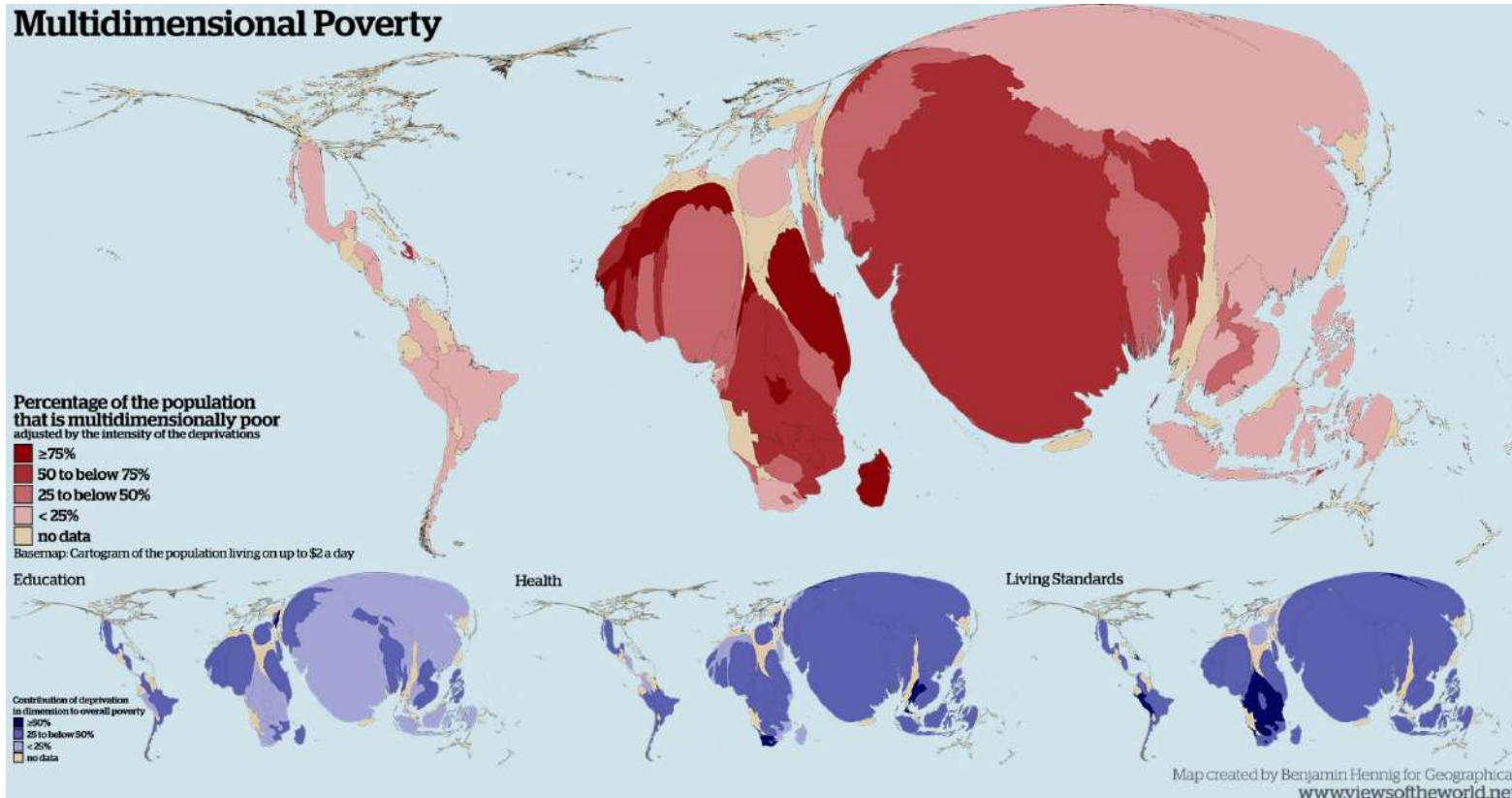


Real-world data e.g. **Electronic Medical Records, health wearables, Internet of Things, digital media, social media**, is combining with scalable technologies and advanced analytics to fundamentally change how and where healthcare is delivered, bridging to the health of populations, and broadening the responsibility for both. It reveals how this shift in healthcare delivery will significantly improve patient outcomes and the health system.

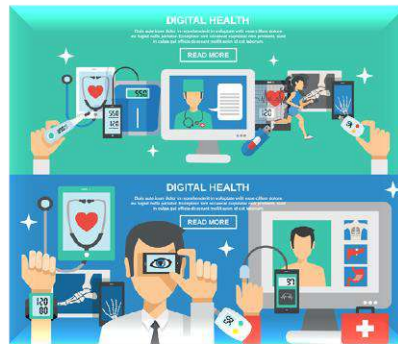
- **Digital innovations**
- **Lean innovations**
- **Around the patient innovation**
- **Value innovation**

HEALTHCARE DISPARITIES

- Will poor have better quality of care with emerging technologies
- Will emerging technologies improve care for those living in poverty expanding quality and lowering costs?



PERSONALIZED MEDICINE. THE OUTLINE OF THE FUTURE



Constant monitoring of
the patient

Remote personal
monitoring

System-biological
models

Proteomic profile

Metabolomic profile

Extrapolation of study
results

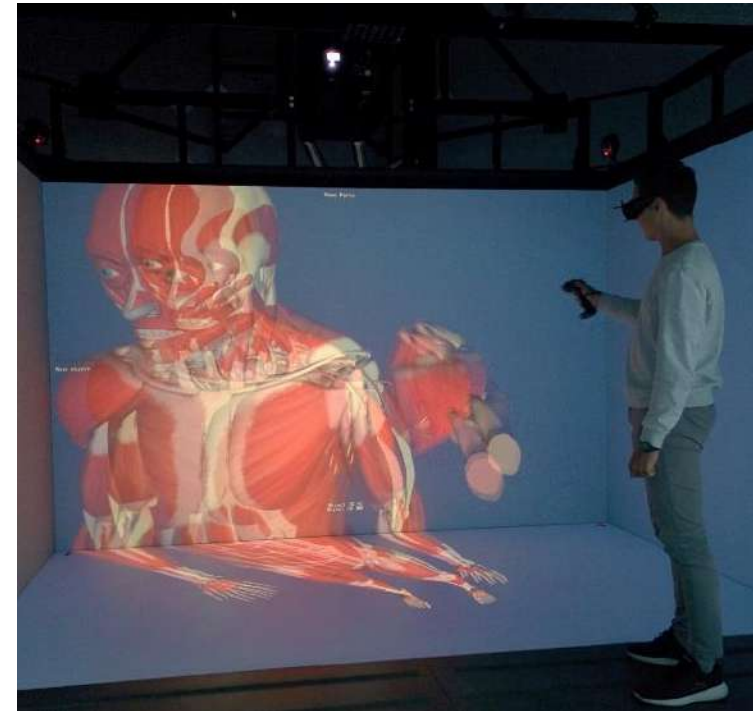


BASHKIR STATE MEDICAL UNIVERSITY AND UFA STATE AIRCRAFT TECHNICAL UNIVERSITY

HIGH-PERFORMANCE COMPUTING CLUSTER (SUPERCOMPUTER)

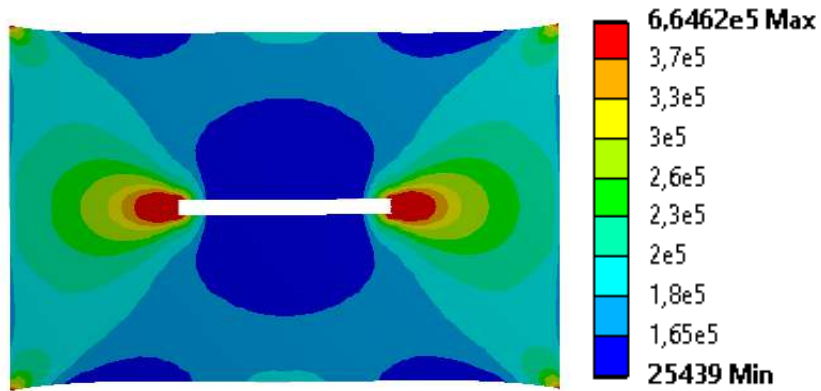


Peak performance ~ 40 TFlops

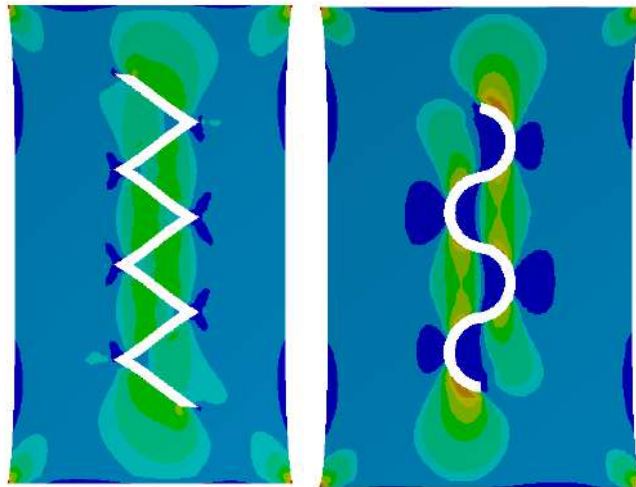


3D-Room
CAVE-type

OPTIMIZATION OF A SCAR AND FLAP GEOMETRY AT STAGE OF PLANNING OF A SURGERY



Dupuytren's contracture

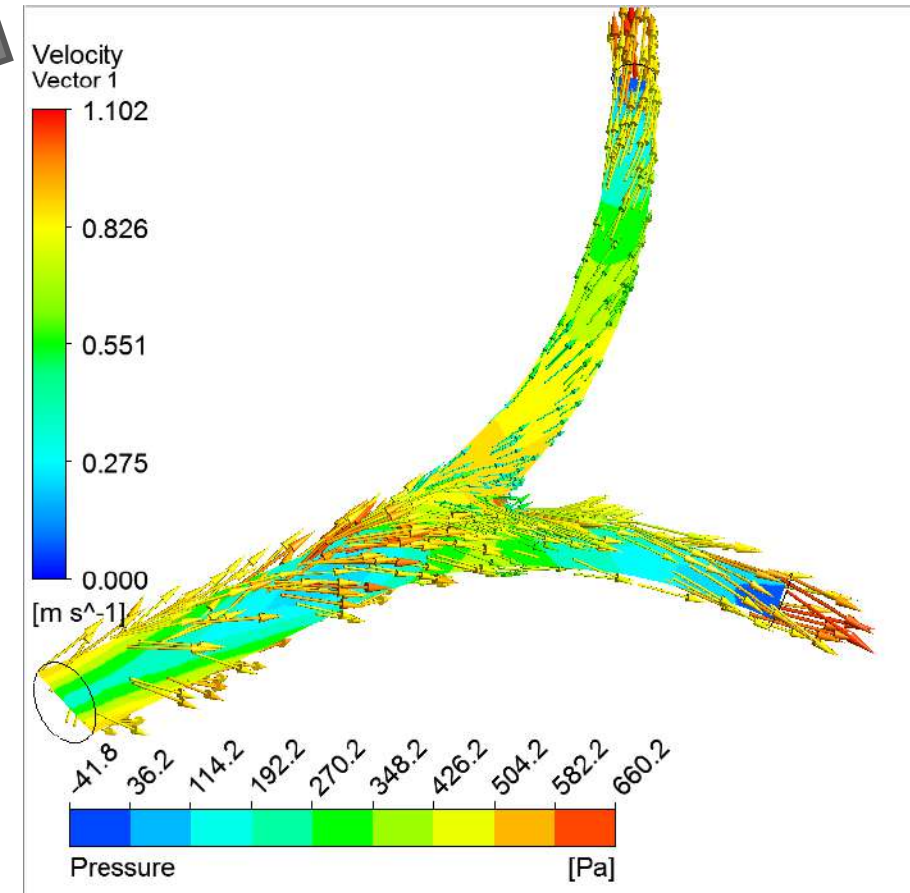
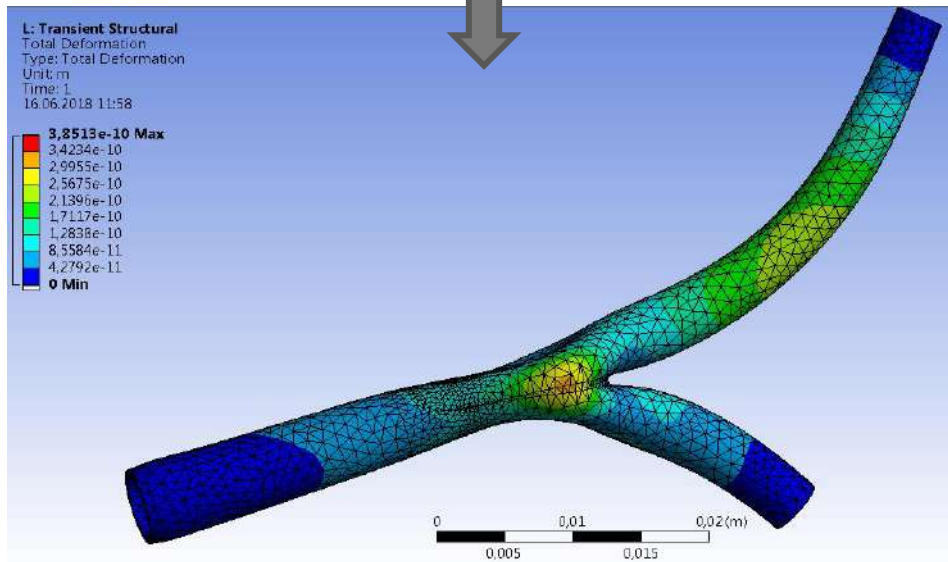


Urothelial carcinoma of the bladder. Reconstructive-plastic restoration of the defect of the anterior abdominal wall by a free thoraco-dorsal flap.

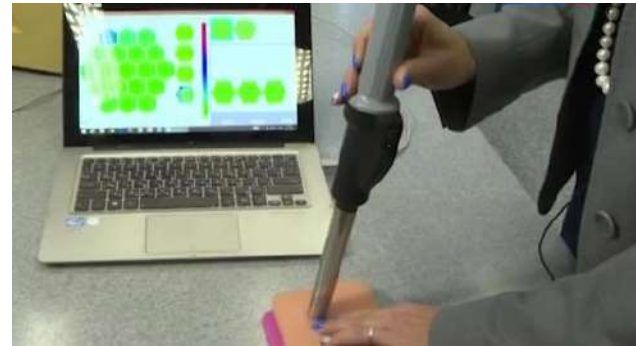
BLOOD FLOW AT THE AORTA

Arterial pressure in the central section of the aorta and the vector field of blood flow velocity

Distribution of aortic wall deformation due to arterial pressure

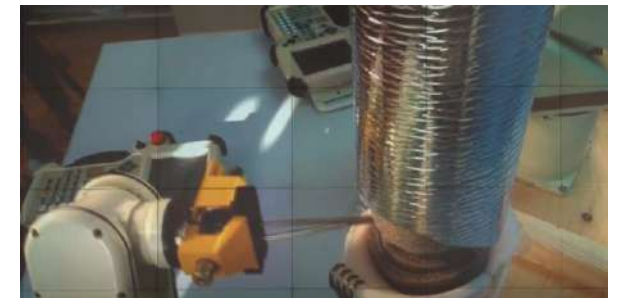


MSU AND BSMU ROBOT-ASSISTING SURGERY COLLABORATION



Medical Tactile Endosurgical complex

Collaboration in the field of robotic surgery, the development of new surgical tools based on mechanoreceptors (Medical Tactile Endosurgical complex. The «digital finger» of a surgeon for intraoperative diagnosis of tumors)



Center for Robotic Surgery Clinic BSMU

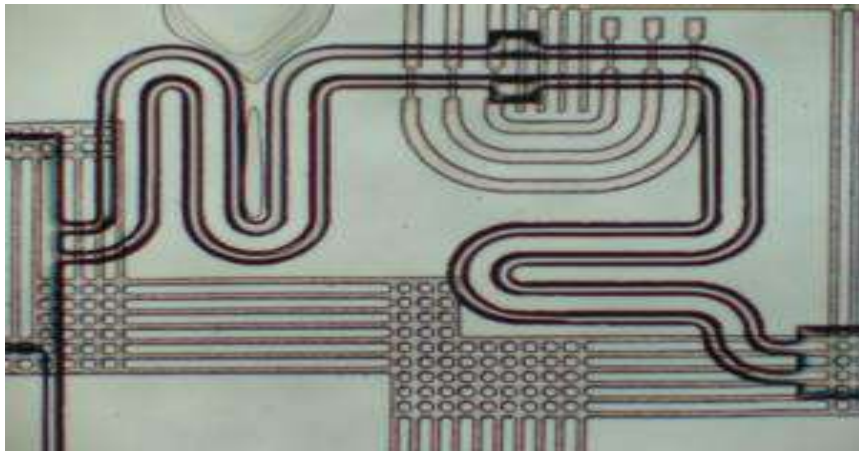
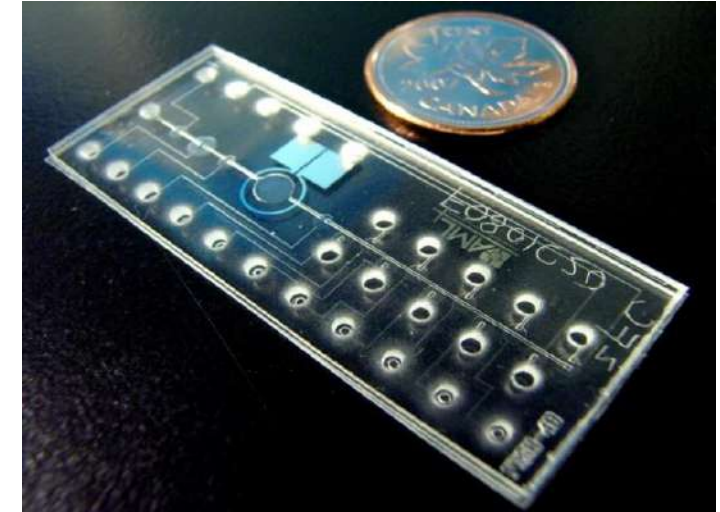
Prototype of the Surgeon-Robot

OPENING OF CENTER OF ROBOTIC SURGERY AND CENTER OF CELL CULTURE IN UNICLINIC OF BSMU (NOVEMBER 2018) WITH PROF. WOLF WIELAND



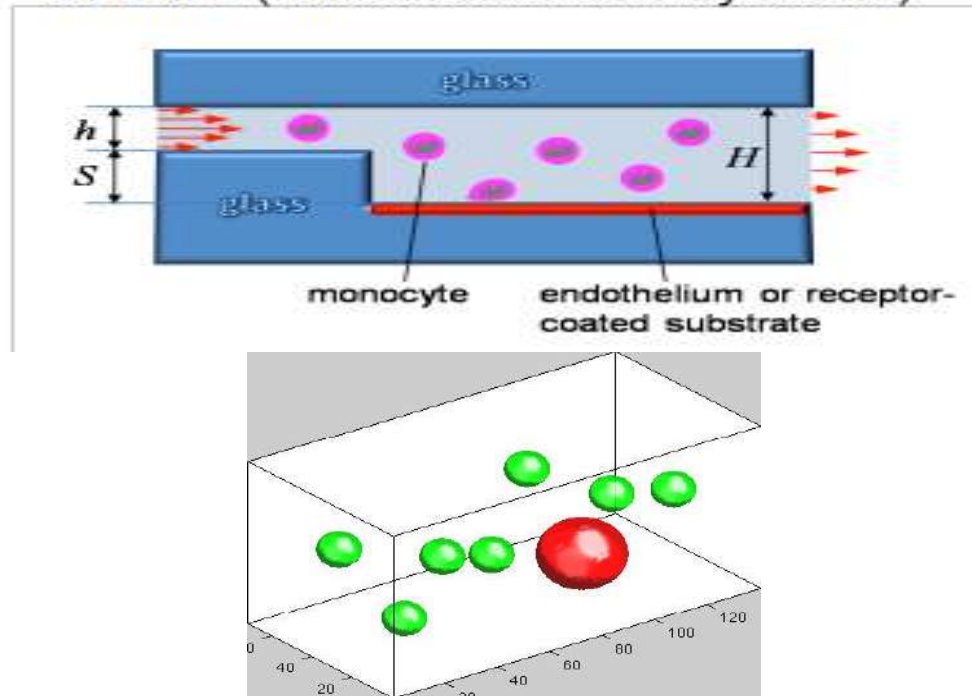
MICROFLUIDICS

Microfluidics is both the science which studies the behavior of fluids through micro-channels, and the technology of manufacturing microminiaturized devices containing chambers and tunnels through which fluids flow or are confined.



Microfluidics deal with very small volumes of fluids, down to femtoliters (fL) which is a quadrillionth of a liter. Fluids behave very differently on the micrometric scale than they do in everyday life: these unique features are the key for new scientific experiments and innovations.

In vitro (microfluidic flow systems)

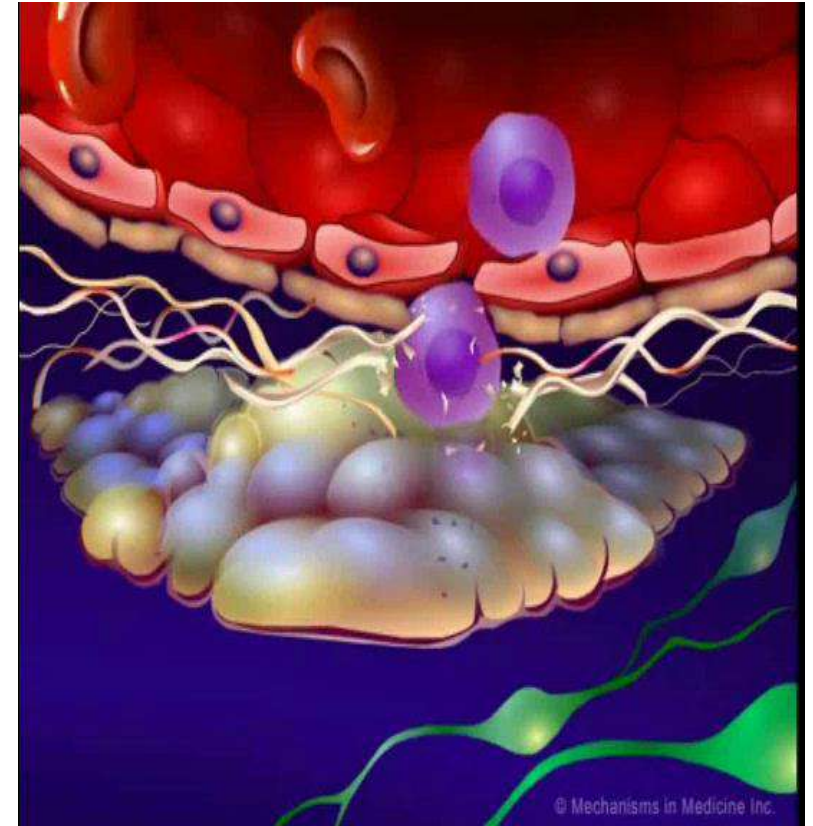
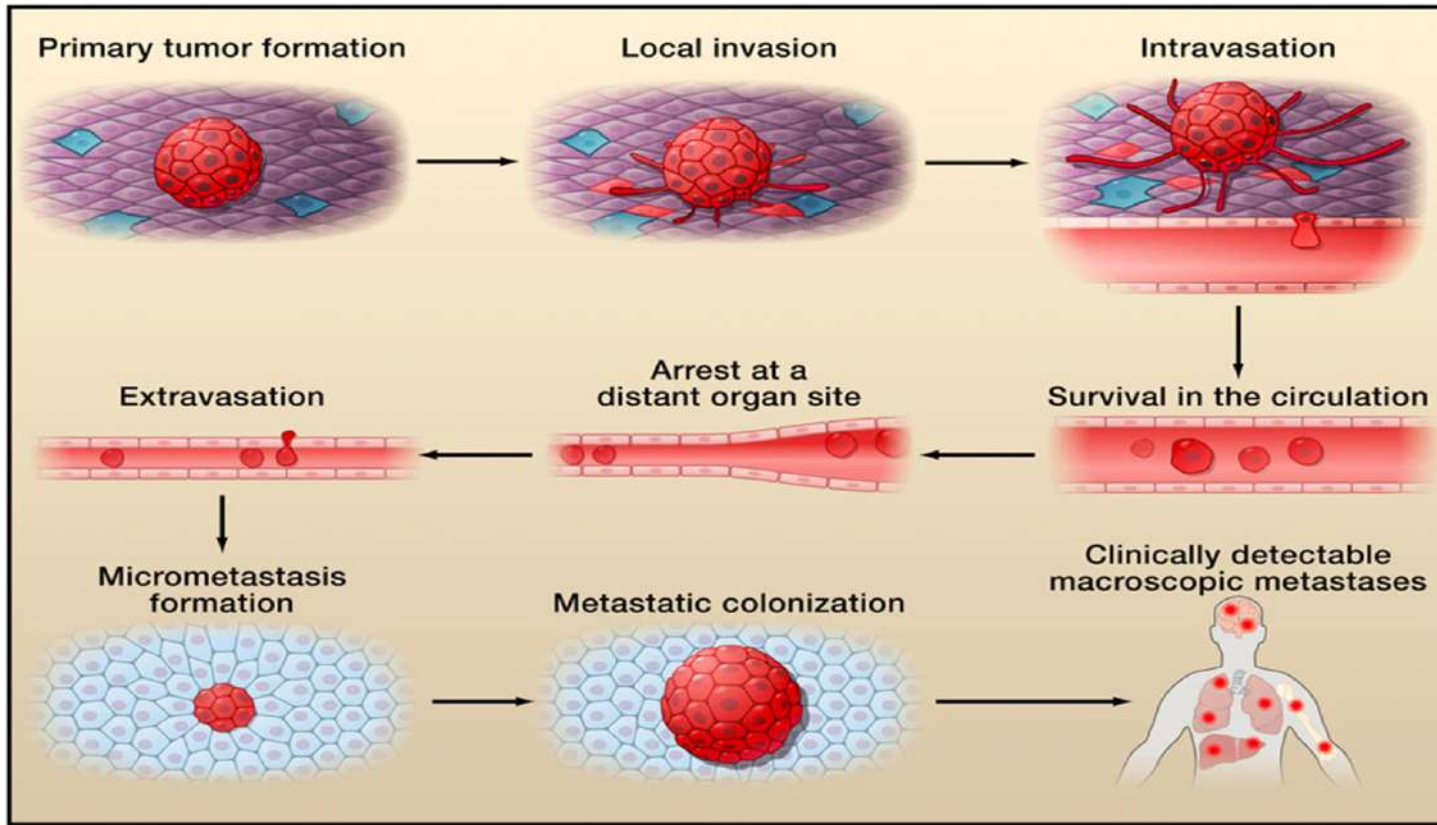


Snapshot of cells migrating in a rectangular micro-channel, according to our numerical simulation. A bigger and less deformable red-colored cell is located closer to the wall than smaller and more deformable green-colored cells.

- **PI: Damir B. Khismatullin, Ph.D.**
Associate Professor
- Project: Quantitative Biomechanical Models of Circulating Cell Interactions

Blood-borne leukocytes (white blood cells) are recruited from peripheral blood into infected tissues during inflammation through a complex series of events involving leukocyte capture by activated (dysfunctional) endothelial cells, leukocyte rolling on and firm adhesion to endothelium, and leukocyte transendothelial migration (diapedesis). Currently, it is not well understood how endothelial dysfunction and associated leukocyte adhesion develop in the body and how these pathophysiological processes can be prevented or blocked without causing dangerous side effects. In our laboratory, we study the adhesion of leukocytes and other circulating cells to dysfunctional vascular or lymphatic endothelium. Our computational algorithm can simulate the dynamics of multiple circulating cells with different deformability and size (left picture).

CANCER METASTASIS



- [1] Khismatullin and Truskey, *Biophys. J.* **102**, 1757 - 1766 (2012)
- [2] Chen and Khismatullin, *Inflammation* **36**, 309-319 (2013)
- [3] Wang and Bennett, *Circ. Res.* **111**, 245 - 259 (2012)
- [4] Jackson, *Nat. Med.* **17**, 1423 - 1436 (2011)

COMPUTATIONAL MODELLING DATA: EFFECT OF CYTOPLASMIC VISCOSITY ON CELL ROLLING

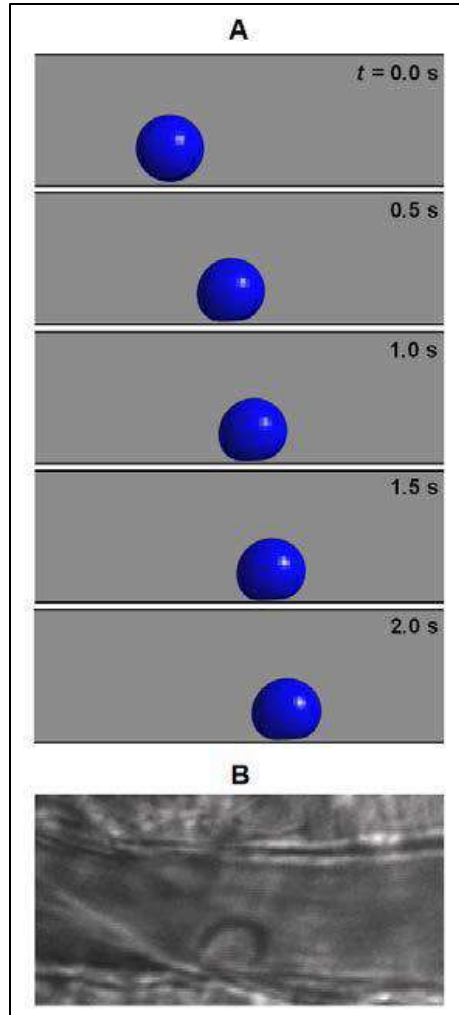
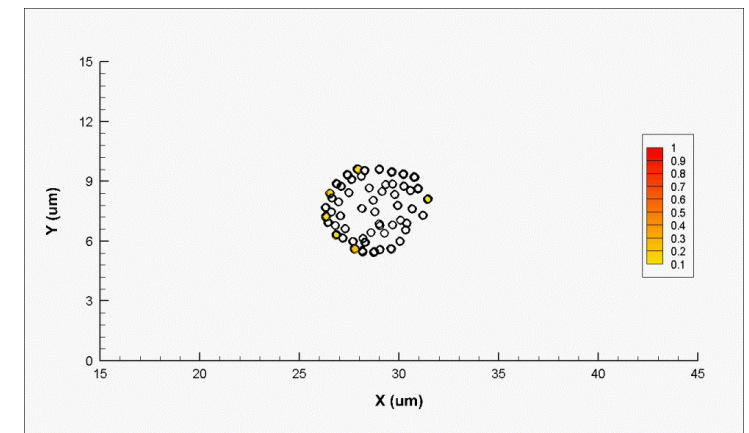
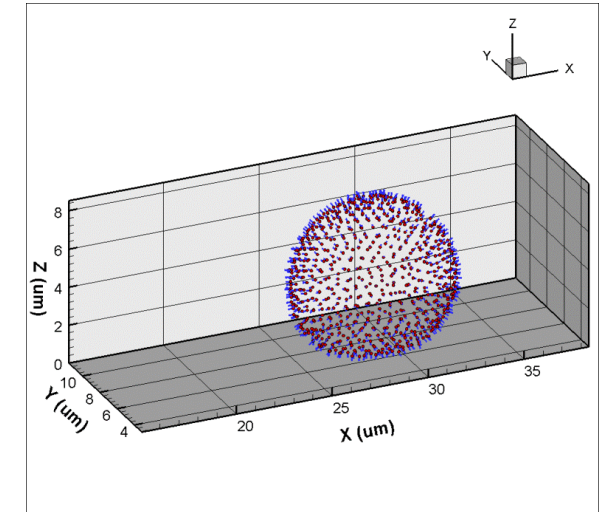
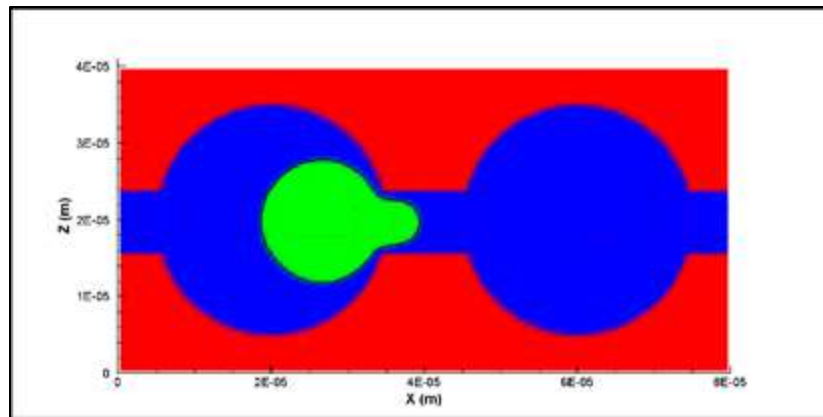
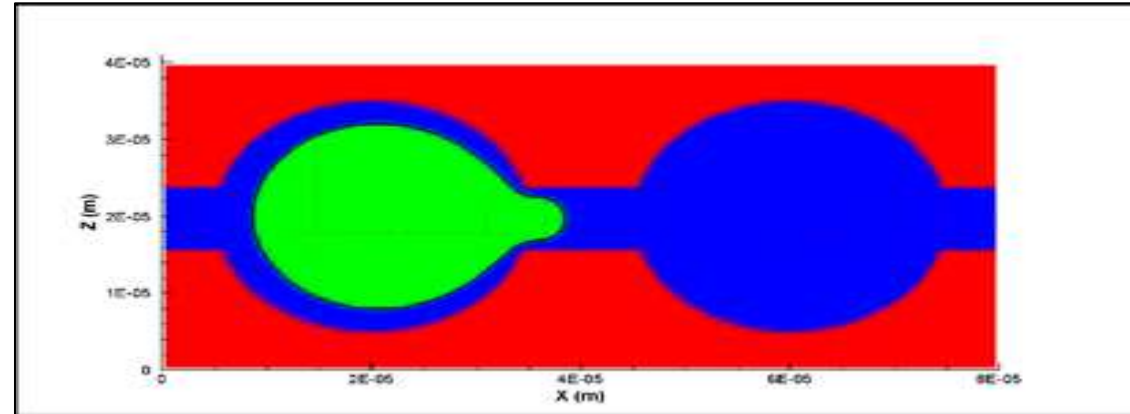
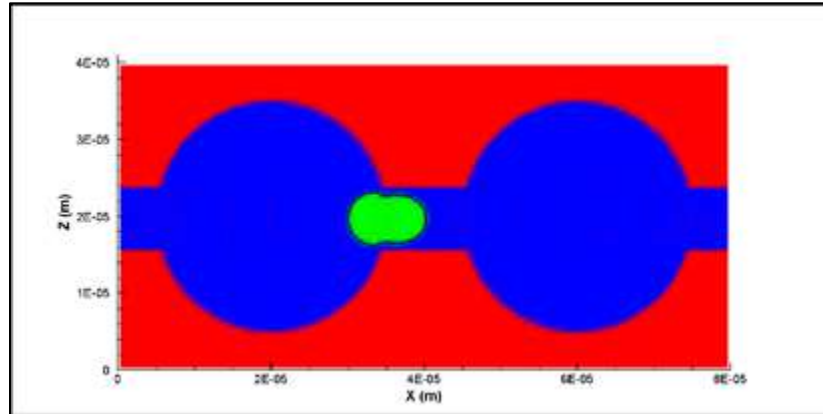


Figure :

- (A) Cell deformation with a cytoplasmic viscosity of $10 \text{ Pa} \cdot \text{s}$ during rolling on the receptor-coated lower surface of the microchannel, according to the VECAM computational algorithm. The shear stress of the wall is 0.05 Pa .
- (B) Leukocyte shape when rolled on the inner surface of a collagen tube coated with endothelium (provided by E. Damiano, Boston U.).

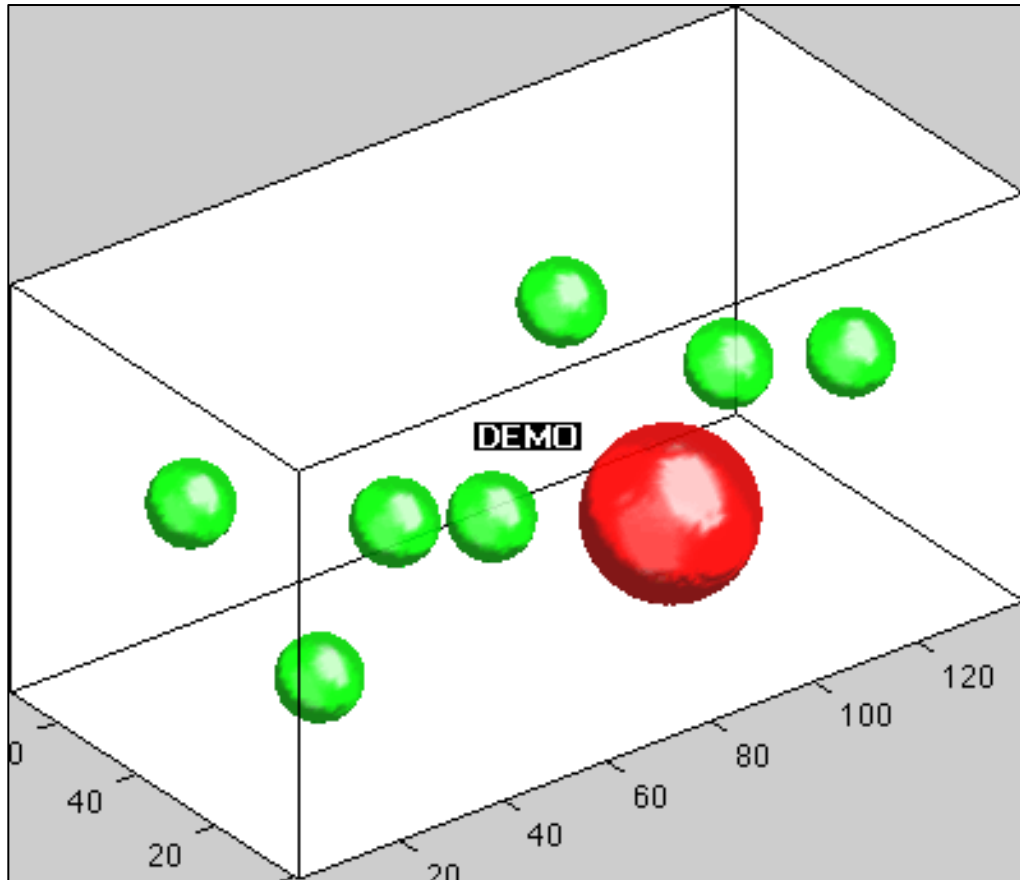


MATHEMATICAL MODEL OF CELL MIGRATION



Deformation of cells of different diameters during passage through a narrowing of $8.1 \mu\text{m}$ in the microchannel, according to the computational model. The ratio of the diameter of the cell to the width of the narrowed section is 1 (at the top), 2 (center) and 3 (bottom).

MATHEMATICAL MODEL OF CELL MIGRATION



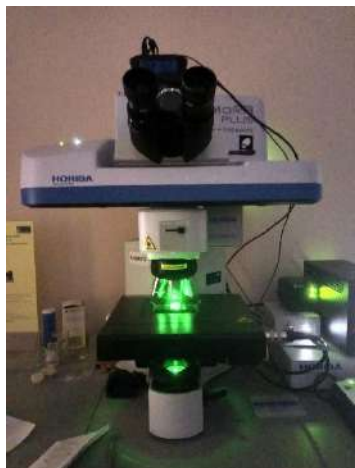
Snapshot of cells migrating in a rectangular micro-channel, according to our numerical simulation. A bigger and less deformable red-colored cell is located closer to the wall than smaller and more deformable green-colored cells. This explains that leukocyte margination and red blood cell aggregation in small vessels are caused by the differences in deformability and size between these types of blood cells.

SPECTROSCOPY OF COMBINATIONAL DISPERSION (RAMAN-SPECTROMETRY)

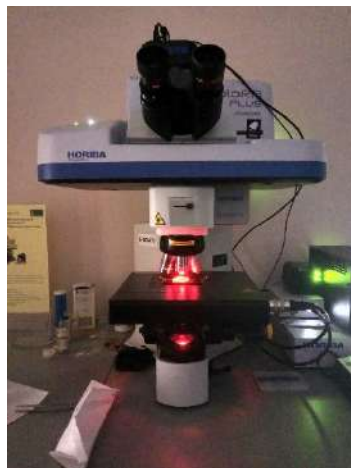
Spectroscopy of combinational dispersion is the method of spectroscopy, which bases on ability of investigated system (molecules) for inelastic (Raman or combinational) dispersion of monochromatic colour.



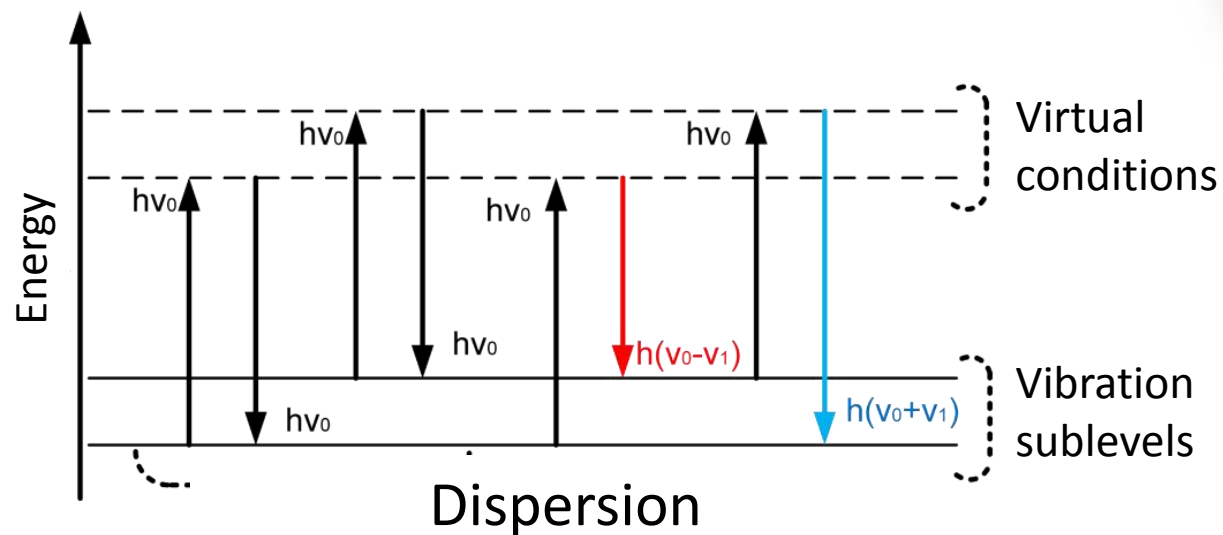
Horiba XploRA plus (Horiba, Ltd., Япония)



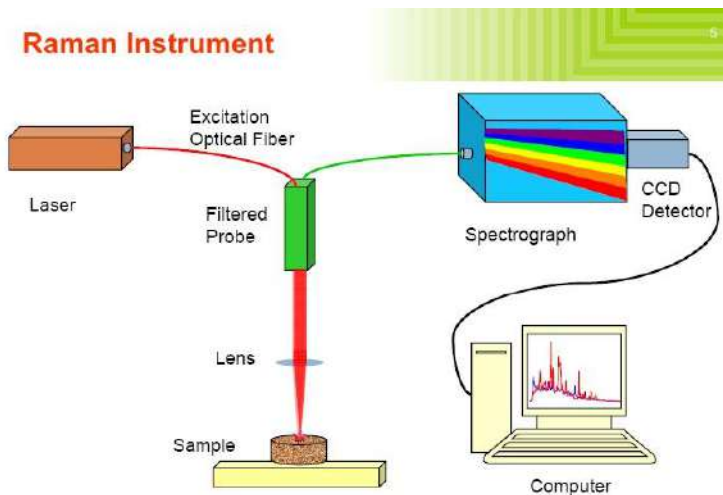
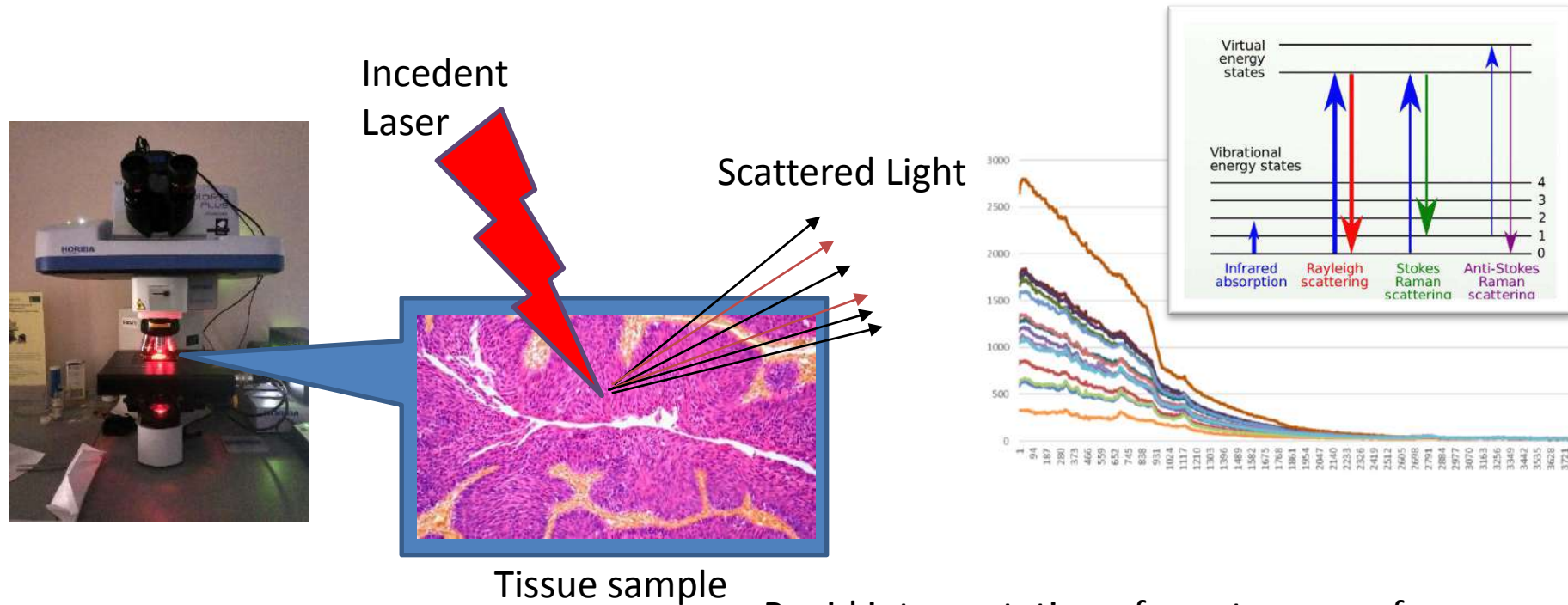
532 nm



638 nm

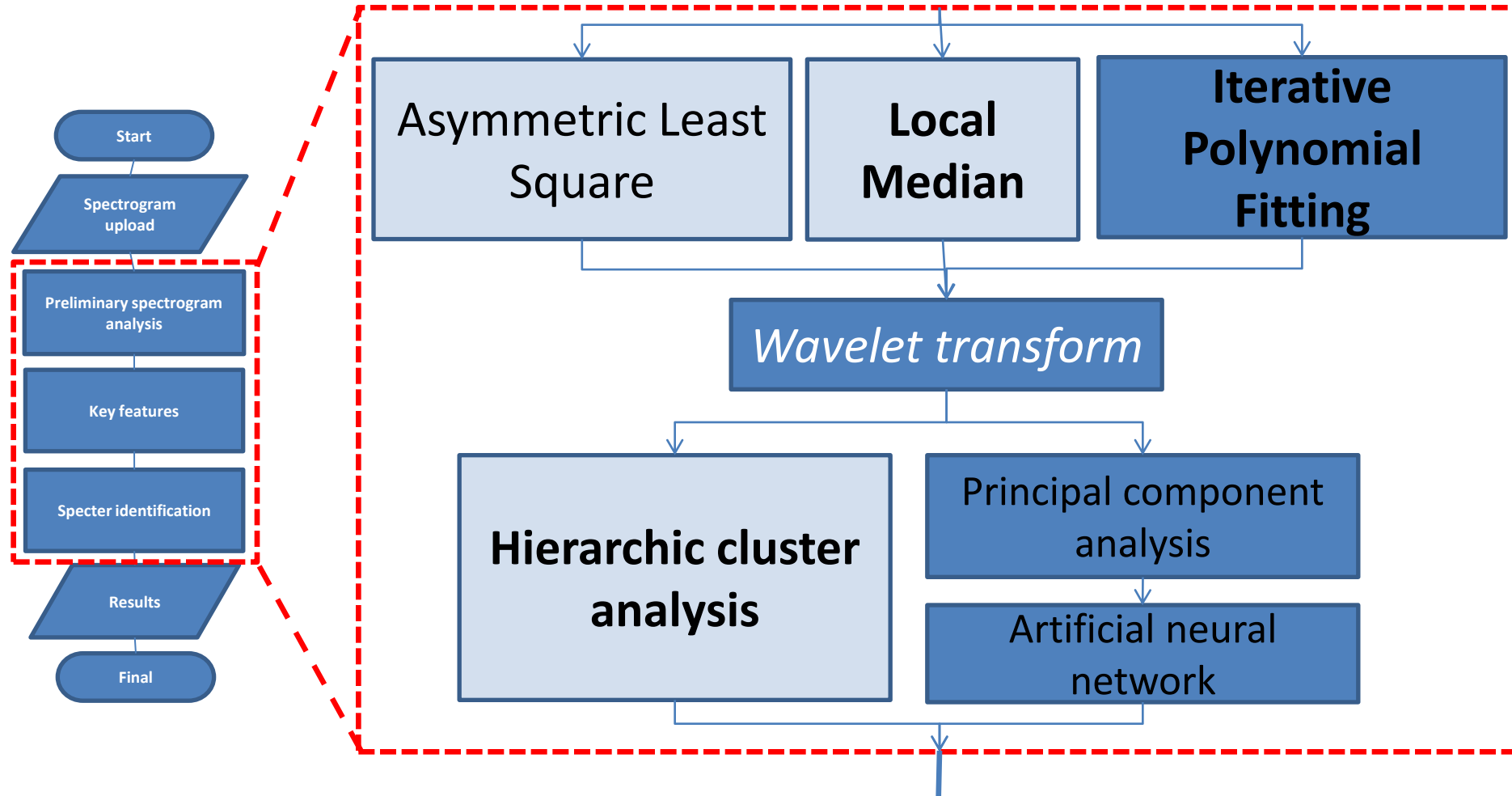


FAST INTERPRETATION OF RAMAN SPECTROSCOPY RESULTS (MACHINE LEARNING AND DATA MINING)

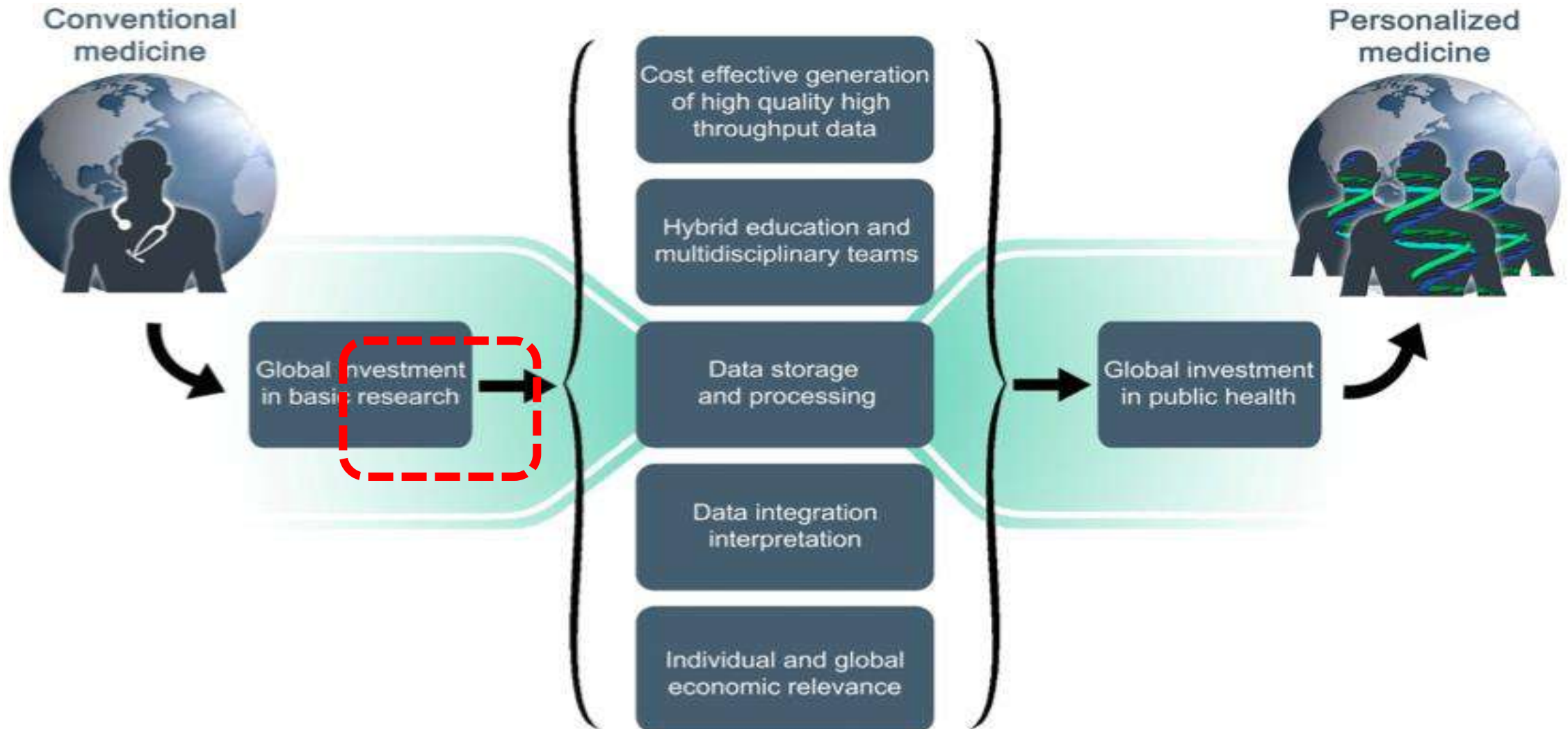


Rapid interpretation of spectrograms for intraoperative pathology diagnostics is not developed. We propose a new algorithm based on a multi-stage mathematical signal processing with the subsequent use of deep learning (neural network). The quality of the solution in many cases is now comparable, and in some cases exceeds the efficiency of "protein" experts.

OPTIMAL ALGORITHM OF CELL DIAGNOSTICS BY RAMAN SPECTROSCOPY



CHALLENGES: FROM POPULATION SCIENCES TO BASIC RESEARCH



THANK YOU FOR ATTENTION!

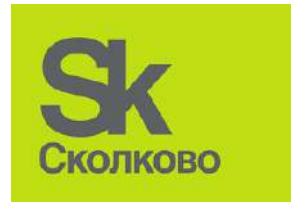


Welcome to Bashkortostan !

OUR TEAM



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