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Kick-off event
Interaction Platform

BIGPICTURE

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ESP Basel, 5.9.2022

Interaction Platform

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Goal:

To provide an interaction platform between the scientific experts, regulatory and health authorities for clinical whole slide images and AI.

Involvement of

- Scientists
- Manufacturers
- Authorities and regulators
- Users
- Patient advocacy groups

Challenges to be addressed

- Digital Pathology and AI is a rapidly developing field
- Lack of experience how regulatory requirements (IVDR) should be applied
- High impact on health care (e.g., precision medicine, companion diagnostics)
- Transition from research and IVD development
- Industry vs. “Lab developed” tests

Regulatory Requirements for IVD in EU

L 117/176 EN Official Journal of the European Union 5.5.2017

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

In force since May 26th 2017

To be applied to all diagnostics on the market and put into service (by manufacturer and lab-developed tests) from May 26th 2022

28.1.2022 EN Official Journal of the European Union L 19/3

REGULATION (EU) 2022/112 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 25 January 2022

amending Regulation (EU) 2017/746 as regards transitional provisions for certain *in vitro* diagnostic medical devices and the deferred application of conditions for in-house devices

New transition period for class C devices on the market May 26th 2026

IVDR *Annex I*
General Safety and Performance Requirements

16. Electronic programmable systems — devices that incorporate electronic programmable systems and software that are devices in themselves

16.1. Devices that incorporate electronic programmable systems, including software, or software that are devices in themselves, shall be designed to ensure repeatability, reliability and performance in line with their intended use. In the event of a single fault condition, appropriate means shall be adopted to eliminate or reduce as far as possible consequent risks or impairment of performance.

16.2. For devices that incorporate software or for software that are devices in themselves, the software shall be developed and manufactured in accordance with the state of the art taking into account the principles of development life cycle, risk management, including information security, verification and validation.

16.3. Software referred to in this Section that is intended to be used in combination with mobile computing platforms shall be designed and manufactured taking into account the specific features of the mobile platform (e.g. size and contrast ratio of the screen) and the external factors related to their use (varying environment as regards level of light or noise).

16.4. Manufacturers shall set out minimum requirements concerning hardware, IT networks characteristics and IT security measures, including protection against unauthorised access, necessary to run the software as intended.

CHAPTER VI CLINICAL EVIDENCE, PERFORMANCE EVALUATION AND PERFORMANCE STUDIES

Article 56 Performance evaluation and clinical evidence

3. A performance evaluation shall follow a defined and methodologically sound procedure for the demonstration of the following, in accordance with this Article and with Part A of Annex XIII:

(a) scientific validity;

(b) analytical performance;

(c) clinical performance.

IVDR: Scientific Validity

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on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

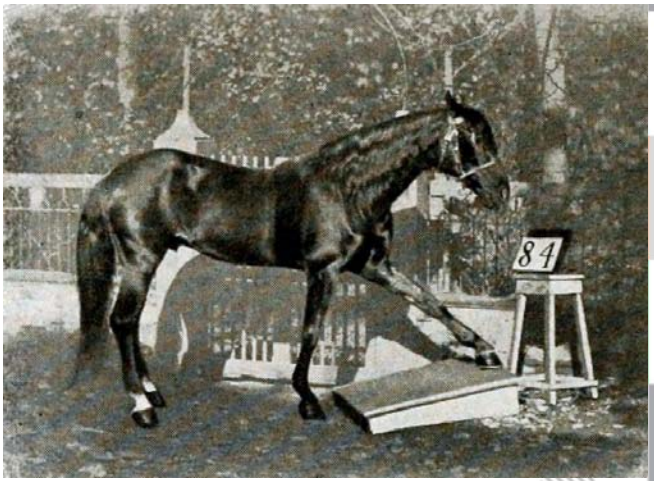
'scientific validity of an analyte' means the association of an analyte with a clinical condition or a physiological state;

→ Features & signatures have to be explained
no "black-box" algorithms

AI and the "Clever Hans" Risk

From Wikimedia

Clever Hans (der Kluge Hans) was a horse famous for his apparent ability to perform mathematical puzzles and tell the answers by knocking his hoof on the ground. It was later revealed that he could not count, but could tell the right answer by the reactions of his audience.



Received: 19 November 2018 | Revised: 26 January 2019 | Accepted: 24 February 2019
DOI: 10.1002/widm.1312

WIREs DATA MINING AND KNOWLEDGE DISCOVERY WILEY

ADVANCED REVIEW

Causability and explainability of artificial intelligence in medicine

Andreas Holzinger[1] | Georg Langs[2] | Helmut Denk[3] | Kurt Zatloukal[3] | Heimo Müller[1,3]

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Explainability: Highlights the decision-relevant parts of the used representations of the algorithms and active parts in the algorithm

Causability : a human expert achieves a specified level of causal understanding

Training of Algorithms has to Include a Broad Spectrum of Data Variables

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Report of UN Secretary-general's high-level Panel on Digital Cooperation:
"Gaps in the data on which algorithms are trained can likewise automate existing patterns of discrimination, as machine learning systems are only as good as the data that is fed to them."

Training data should include:

- Various disease types and comorbidities
- Various pre-analytical variabels and artefacts
- Data from different populations

IVDR *Annex I*
General Safety and Performance Requirements

GENERAL REQUIREMENTS

3. Manufacturers shall establish, implement, document and maintain a risk management system (for each device)

REQUIREMENTS REGARDING PERFORMANCE, DESIGN AND MANUFACTURE

9. Performance characteristics

9.1. Devices shall be designed and manufactured in such a way that they are **suitable for the purposes**

(a) **the analytical performance**, such as, analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness and precision), limits of detection and quantitation, measuring range, linearity, cut-off, including determination of appropriate criteria for specimen collection and handling and control of known relevant endogenous and exogenous interference, cross-reactions; and

(b) **the clinical performance**, such as diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, expected values in normal and affected populations.

IVDR *Annex I*
General Safety and Performance Requirements

What does this mean for digital pathology and AI?
Specimen ~ slide for scanner
Specimen is ~ data for AI

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(b) **the clinical performance**, such as diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, expected values in normal and affected populations.

Implication of the Intended Purpose

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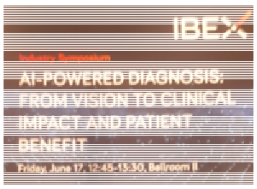
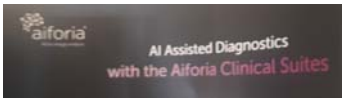
Examples of how digital pathology and AI products are marketed





- Improved workflows
- Improved diagnosis
- Decision support
- Improved patient benefit

IVDs Manufactured by Industry and within Health Institutions

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Implications of manufacture and use of devices within the same health institution ('in-house devices') "lab developed tests"

4. Devices that are manufactured and used within health institutions, with the exception of devices for performance studies, shall be considered as having been put into service.

Final responsibility for IVDR compliance of the whole diagnostic workflow is with the user that makes the diagnosis

Next Steps

- Collection of critical issues
- Discussion of issues identified
- Production of consensus reports
- Dissemination

Format:

- Virtual and F2F meetings

Acknowledgement

BBMRI.AT Biobanking and BioMolecular Resources Research Infrastructure Austria
Funded by: BMBWF-10.470/0010-V/3c/2018 (2018-2023)

BBMRI-ERIC Biobanking and BioMolecular Resources Research Infrastructure

ADOPT BBMRI-ERIC gateway for health
Project number: 676550

BBMRI GA Nr. 212111
1.2.2008-30.04.2010

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Thank You for Your Attention!