PIPELINE OF NEW DIAGNOSTIC METHODS

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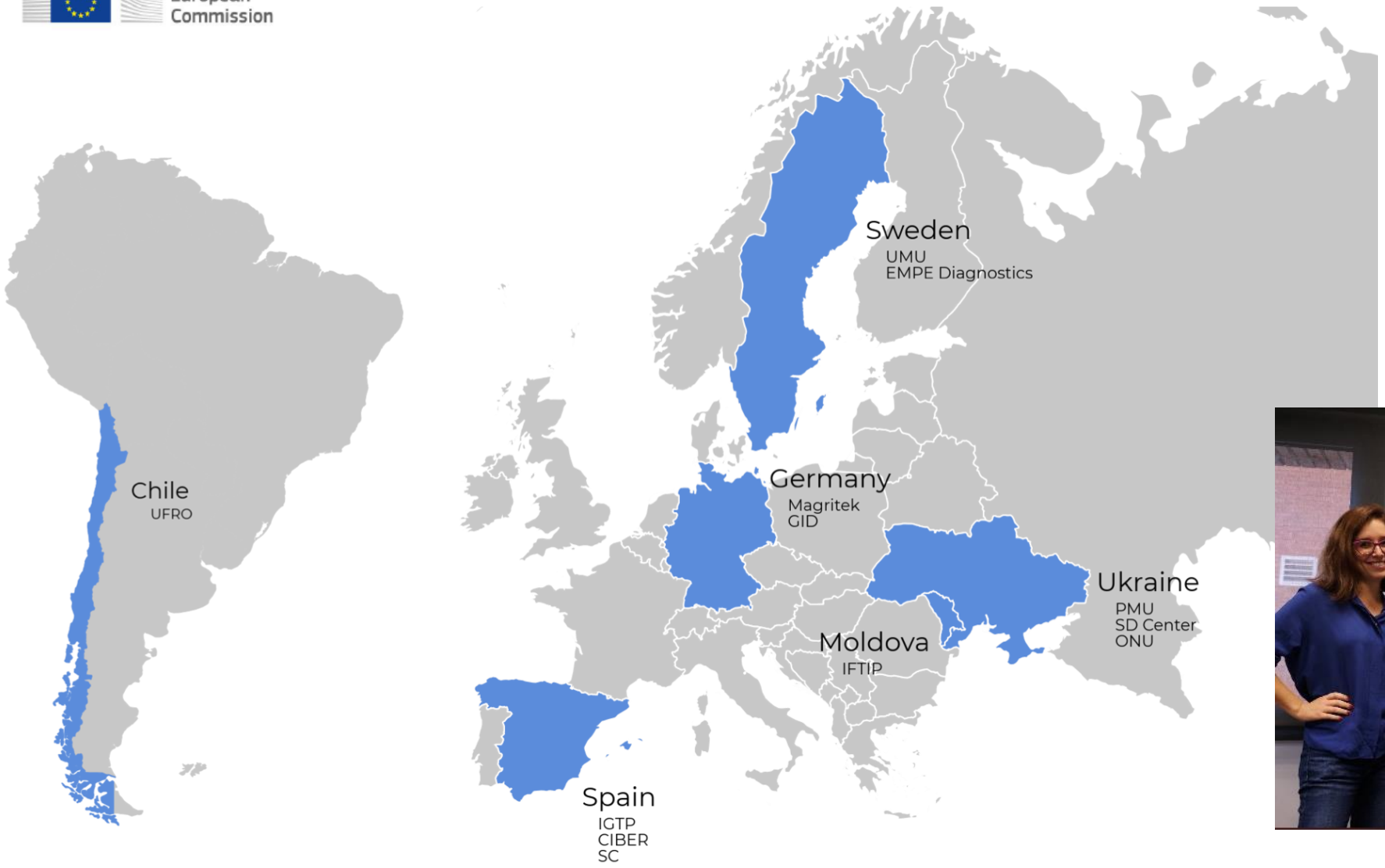
IGTP Germans Trias i Pujol Research Institute

INNOVA4TB

SUMMARY

1. INNOVA4TB Consortium: Who we are?
2. Current methods: Why new methods?
3. Novelties in diagnostics: What is coming?
4. Final conclusions
5. Q&A

European Commission



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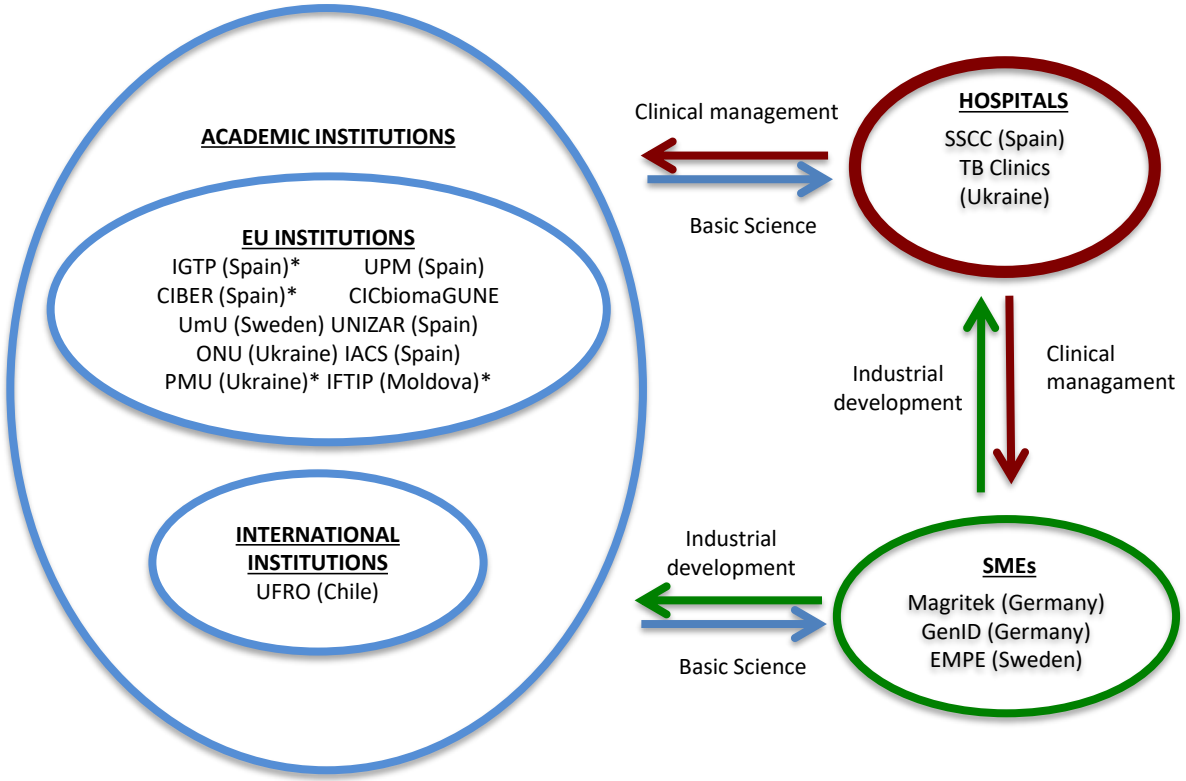
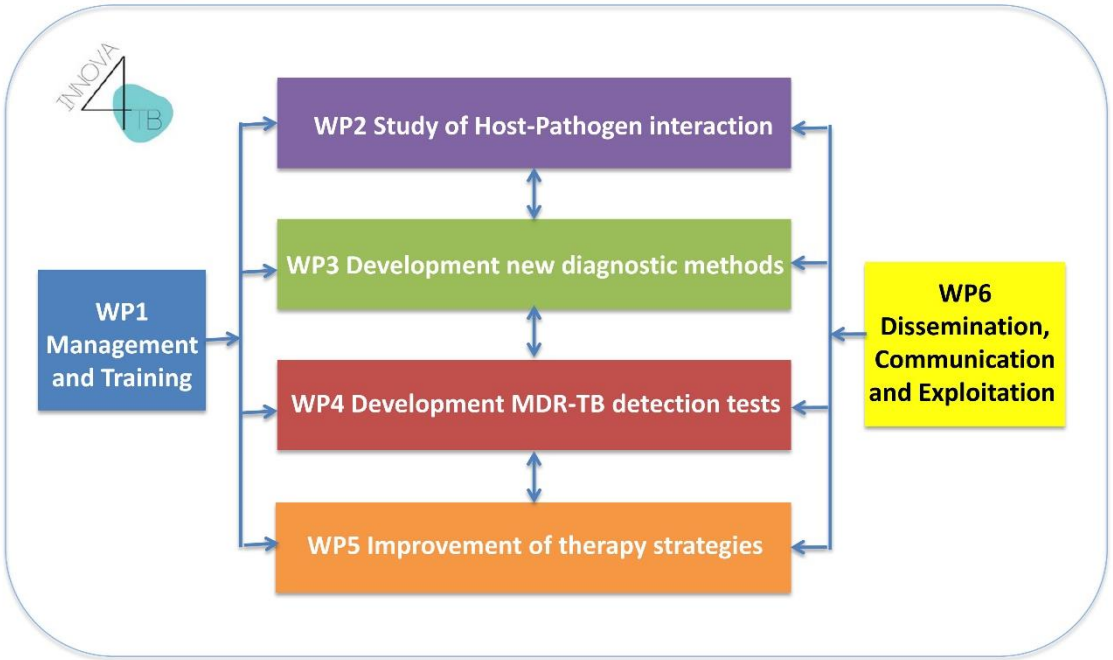

ACADEMIC INSTITUTIONS
EU INSTITUTIONS
IGTP (Spain)* UPM (Spain)
CIBER (Spain)* CICbiomaGUNE
UmU (Sweden) UNIZAR (Spain)
ONU (Ukraine) IACS (Spain)
PMU (Ukraine)* IFTIP (Moldova)*
INTERNATIONAL INSTITUTIONS
UFRO (Chile)
Clinical management
Basic Science
HOSPITALS
SSCC (Spain)
TB Clinics
(Ukraine)
Industrial development
Clinical managament
Industrial development
Basic Science
SMEs
Magritek (Germany)
GenID (Germany)
EMPE (Sweden)


WP2 Study of Host-Pathogen interaction
WP3 Development new diagnostic methods
WP1 Management and Training
WP4 Development MDR-TB detection tests
WP6 Dissemination, Communication and Exploitation
WP5 Improvement of therapy strategies

INNOVA4TB: Training programme

Early-Stage Researcher

Experienced Researcher

1-12 months

International

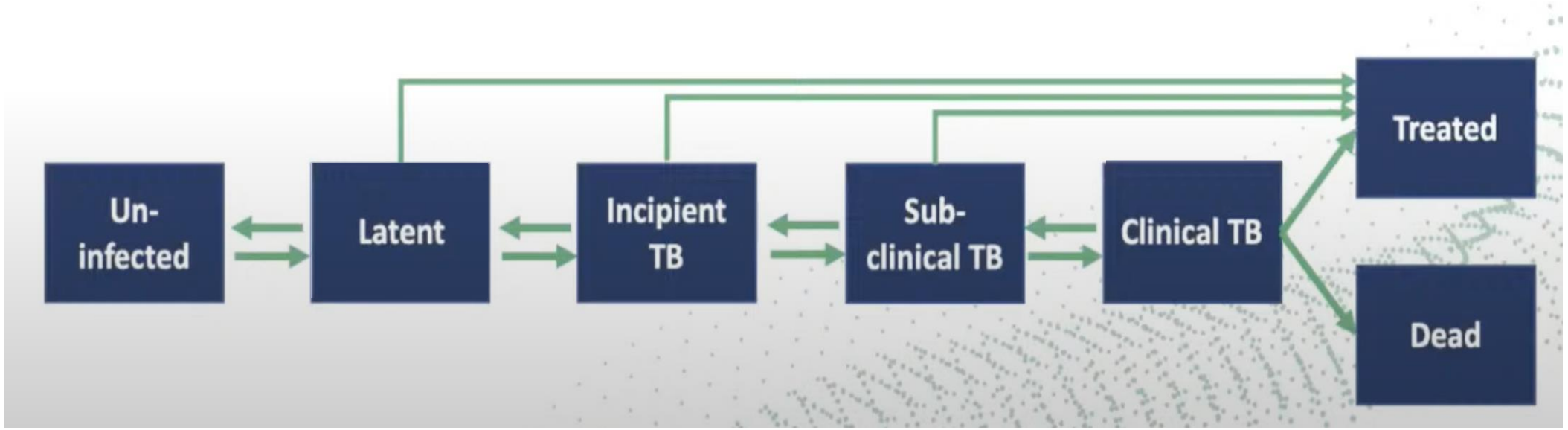
Intersectoral

International Mentor

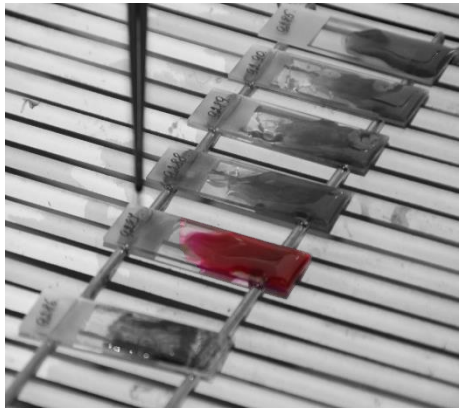
International Supervisor

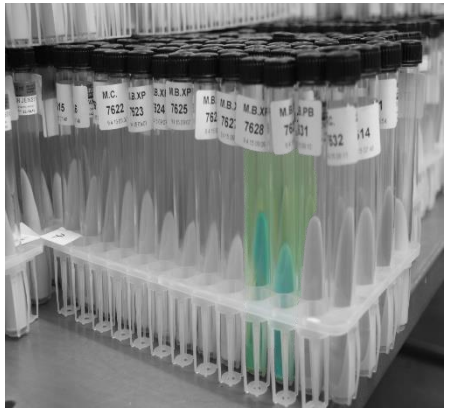
Scientific and Transversal skills

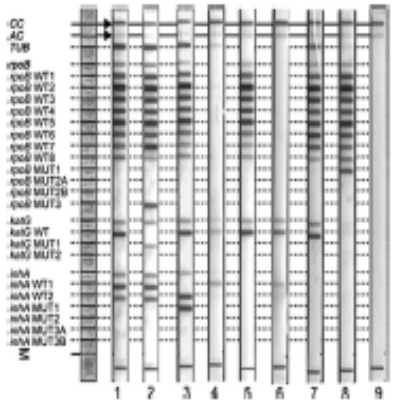
TB AS A SPECTRUM

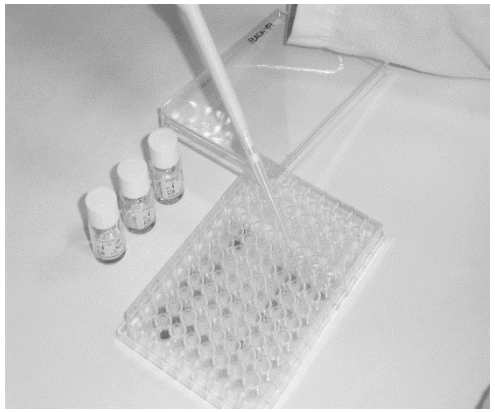


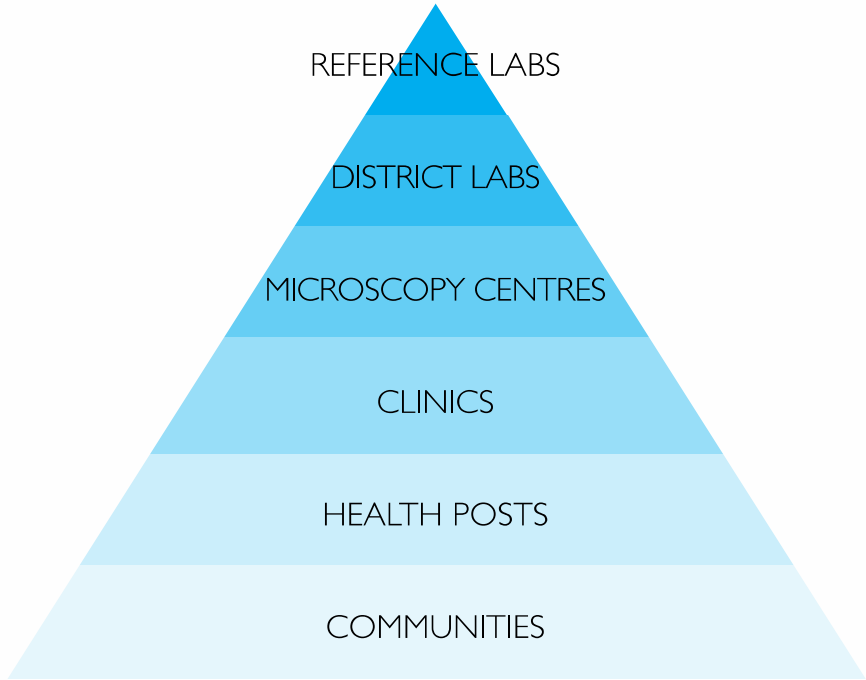
CURRENT TB DIAGNOSTIC METHODS



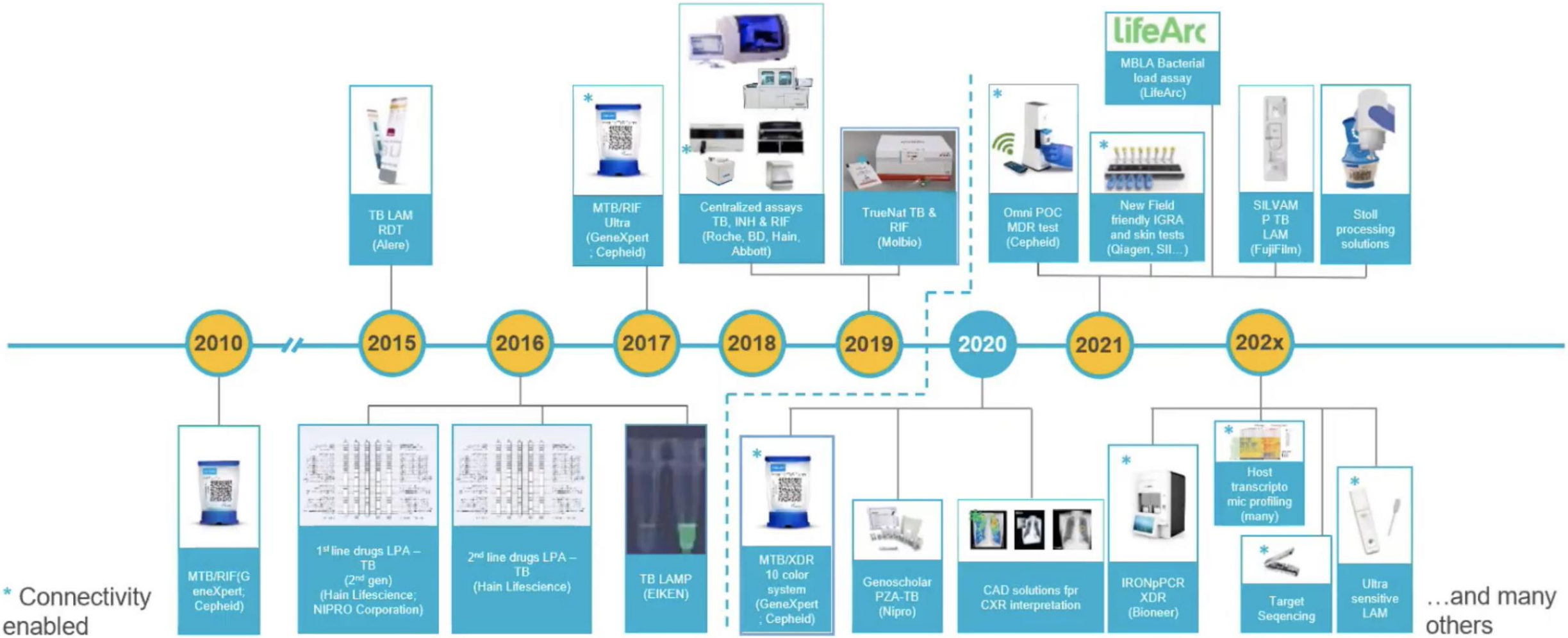








A RICH PIPELINE OF CONNECTED TB DIAGNOSTICS



Adapted from M.Ruhwald

LATENT TB INFECTION

NEW SKIN TESTS

Newer skin tests may improve test specificity and scalability; the evidence has not been systematically reviewed

CTb (Serum Institute of India)

- Recombinant proteins produced in *Lactococcus lactis*

Diaskintest (Generium)

- Recombinant proteins produced in *E Coli*

ESAT6-CFP10 (Anhui Zhifei Longcom)

- Recombinant fusion proteins produced in *E Coli*

NOVELTIES IN IGRAS

Oxford Immunotec

PROGRESSION TO TB

INCIPIENT / SUBCLINICAL TB

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-020-1076-0

Discovery and validation of a personalized risk predictor for incident tuberculosis in low transmission settings

Rishi K. Gupta[1], Claire J. Calderwood[1], Alexei Yavlinsky[2], Maria Krutikov[1], Matteo Quartagno[3], Maximilian C. Aichelburg[4], Neus Altet[5,6], Roland Diel[7,8], Claudia C. Dobler[9,10], Jose Dominguez[11,12,13], Joseph S. Doyle[14,15], Connie Erkens[16], Steffen Geis[17], Pranabashis Haldar[18], Anja M. Hauri[19], Thomas Hermansen[20], James C. Johnston[21], Christoph Lange[22,23,24,25], Berit Lange[26], Frank van Leth[24,27,28], Laura Muñoz[29], Christine Roder[14,15], Kamila Romanowski[21], David Roth[21], Martina Sester[24,30], Rosa Sloot[31], Giovanni Sotgiu[24,32], Gerrit Woltmann[18], Takashi Yoshiyama[33], Jean-Pierre Zellweger[24,34], Dominik Zenner[1], Robert W. Aldridge[2], Andrew Copas[1,3], Molebogeng X. Rangaka[1,3,35,36], Marc Lipman[37,38,40], Mahdad Noursadeghi[39,40] and Ibrahim Abubakar[1,40]

PERISKOPE-TB STUDY

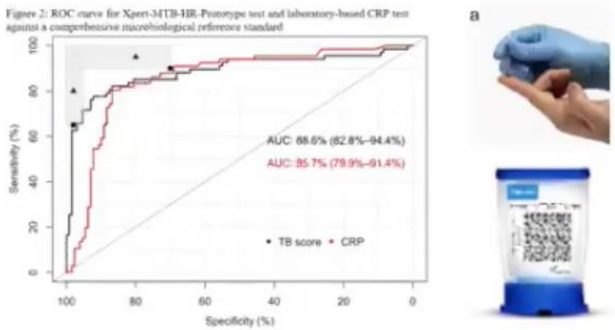
The final prediction model included: **age**, a composite **'TB exposure' variable** (modelled with time-varying covariates to account for non-proportional hazards), **time since migration** for migrants from high TB burden settings, **HIV status**, receipt of a solid **organ or haematological transplant**, normalised percentile **LTBI test result** and commencement of **preventative treatment**

HOST mRNA SIGNATURES

EXTENSIVE WORK IN BASIC SCIENCE STARTING TO YIELD FIRST PRODUCTS

Cepheid Host Response cartridge

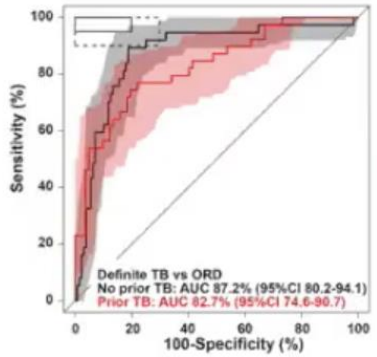
- Using the Sweeny3 signature
- Finger-stick blood, 30min run time
- Explored for
  - Screening test for subclinical and clinical TB (AUC 0.89)
  - Treatment monitoring tool
  - Risk of developing TB

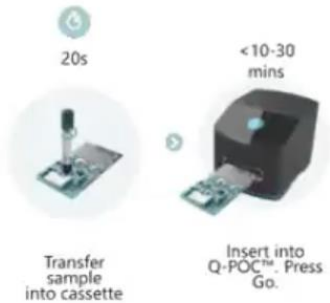


Sweeney et al, Lancet Respiratory Medicine 2016
Södersten et al JCM in press
Zimmer A, Khatri P, Denkinger C *et al* in prep.

QuantuMDx – RISK6 signature

- Based on SATVI RISK6
- Finger-stick blood, 30 min run time
- Explored for
  - Screening test for subclinical and clinical TB
  - Treatment monitoring tool
  - Risk of developing TB



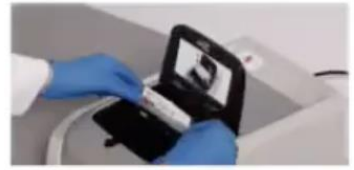


Penn-Nicholson A et al, Scientific Reports 2020
www.quantumdx.com

Biomérieux FilmArray® transcriptomic assay

- 30 marker panel, based on O'Garra
- Filmarray pouch assay on the Biofire platform
- Explored for
  - Screening/triage test for TB
  - Treatment response marker

Sensitivity ~93%
Specificity ~ 94%



Berry M et al Nature 2010, Bloom CI et al Plos One 2012,
Singhania A et al Nature Comms 2018, Singhania A et al Nat. Immunol 2018, www.biomerieux.com

FIND
Because diagnosis matters

Adapted from M.Ruhwald

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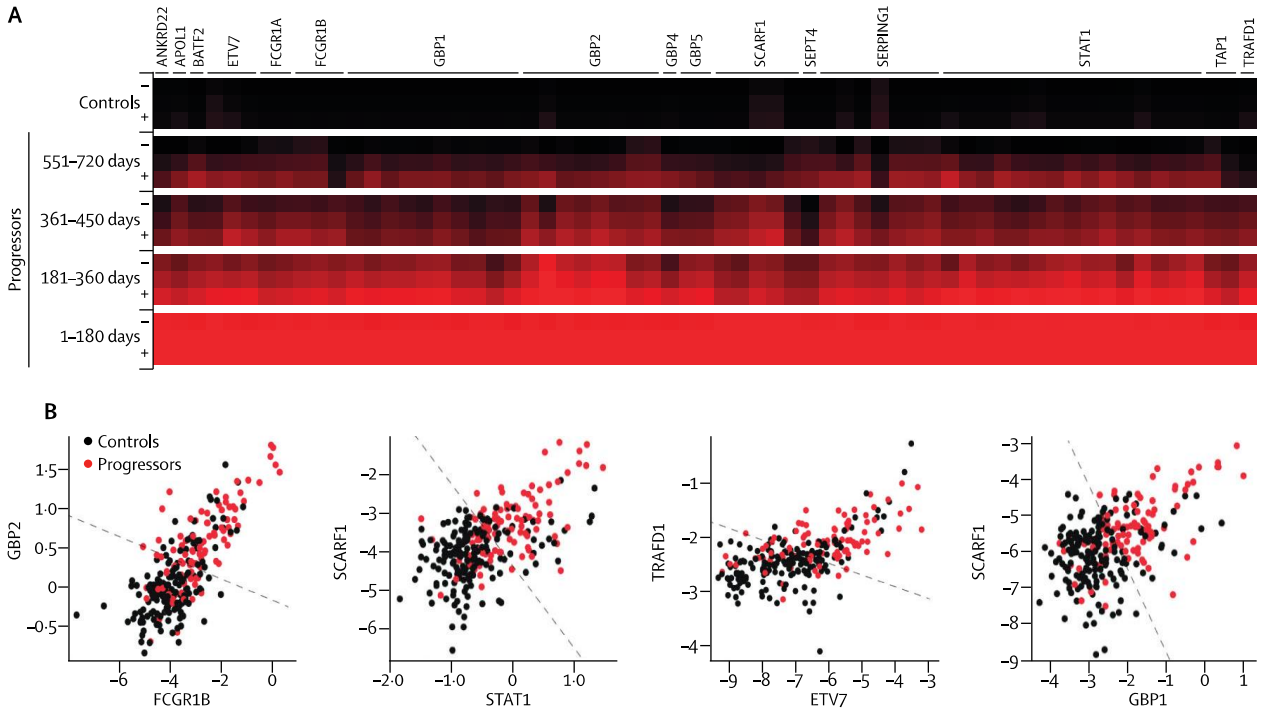
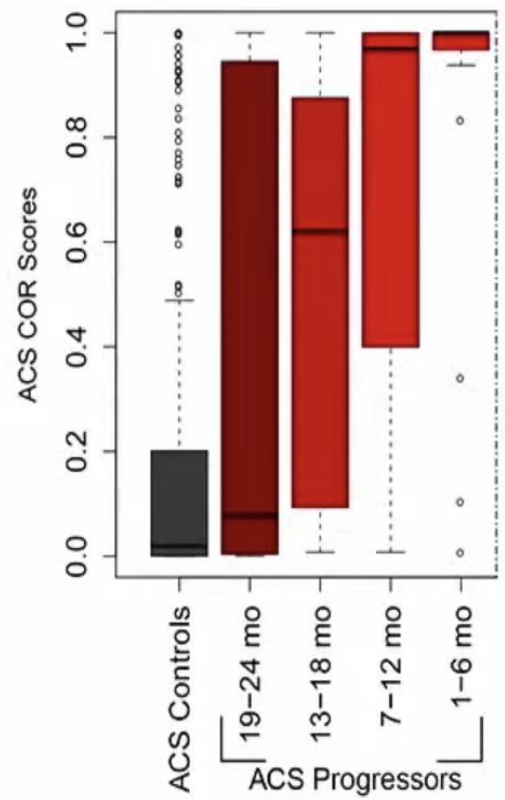
A blood RNA signature for tuberculosis disease risk: a prospective cohort study

Daniel E Zak, Adam Penn-Nicholson*, Thomas J Scriba*, Ethan Thompson†, Sara Suliman†, Lynn M Amon, Hassan Mahomed, Mzwandile Erasmus, Wendy Whatney, Gregory D Hussey, Deborah Abrahams, Fazlin Kafaar, Tony Hawkridge, Suzanne Verver, E Jane Hughes, Martin Ota, Jayne Sutherland, Rawleigh Howe, Hazel M Dockrell, W Henry Boom, Bonnie Thiel, Tom H M Ottenhoff, Harriet Mayanja-Kizza, Amelia C Crampin, Katrina Downing, Mark Hatherill, Joe Valvo, Smitha Shankar, Shreemanta K Parida, Stefan H E Kaufmann, Gerhard Walzl, Alan Aderem, Willem A Hanekom, for the ACS and GC6-74 cohort study groups‡*



Lancet 2016; 387: 2312–22



RISK11 Prognostic Performance

→ 15 months (AUC 0.63): **Poor**

→ 12 months (AUC 0.80): **Moderate**

→ 6 months (AUC 0.95): **Excellent**

TB SCIENCE 2020

Comm. T. Scriba

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ACTIVE TB

DIGITAL X-RAY

JLK inspection

Delft Light

FujiFilm CalneoXair

POC MOLECULAR DIAGNOSTIC METHODS

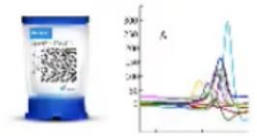
MOLBIO Trueprep + Truelab + Truenat

- First POC molecular diagnostic on the market
- MTB, MTB+, RIF chips already in use in India
- Work on additional assays / validation ongoing

WHO policy: Truenat MTB or MTB Plus may be used as an initial diagnostic test for TB

OMNI & Ultra cartridge

- Integrated processing from sample to result
- Small, portable, in-built connectivity
- Proven cartridge technology
- FIND studies on Omni ongoing



WHO review of Omni and Ultra cartridge planned for 2021

Adapted from M.Ruhwald

CENTRALIZED MOLECULAR DIAGNOSTICS

- Enable
  - high-throughput testing
  - upfront INH testing
  - multi-disease testing
- Comparative analytical study
  - Sensitivity similar to Xpert
  - Resistance detection similar to LPA

Abbott

Abbott *m*2000sp

Abbott *m*2000rt

Hain

GenoXtract®96

FluoroCycler® 96

BD

BD MAX™

Roche

Roche: cobas® 8800/6800 System

Bioneer

Bioneer: ExiStation™ Universal MDx System

De Vos et al. Abstract 1027: Comparative analytical evaluation of four centralized platforms for the detection of M. tuberculosis complex and detection of resistance to rifampicin and isoniazid

FIND Because diagnosis matters

Adapted from M.Ruhwald

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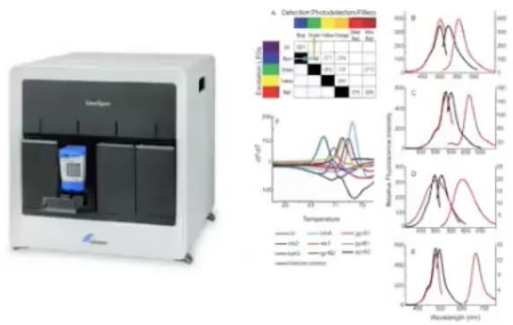
NEW CARTRIDGE BASED ASSAYS WITH BROADER DST PROFILE

Cepheid



Cepheid XDR
10 colour module

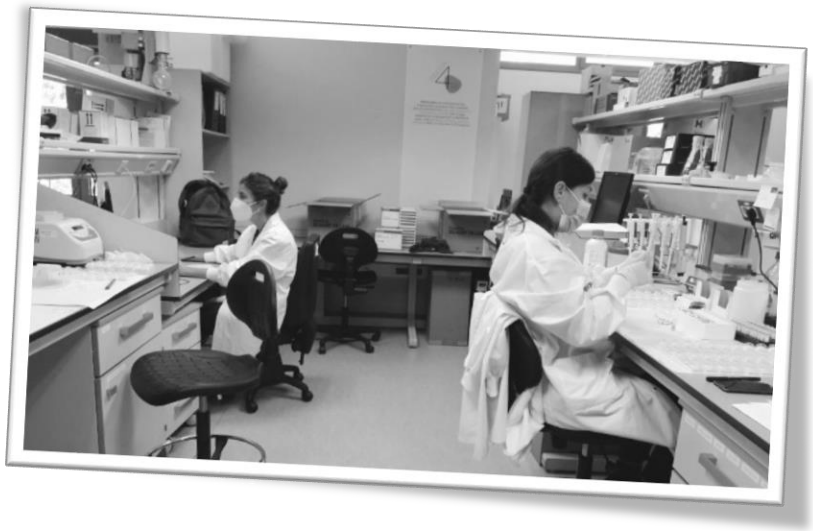
SD Biosensor

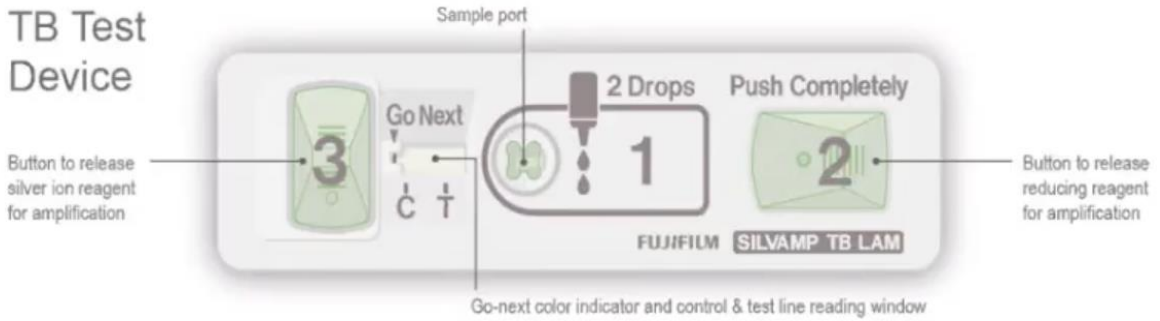
Standard M MDR-TB

Bioneer

IRON-qPCR

FUJILAM SILVAMP TB LAM





IGTP-Nigeria	FujiLAM		
	All HIV Status	HIV Negative	HIV Positive
Sensitivity	68.2% (30/44)	65.7% (23/35)	77.8% (7/9)
Specificity	96.8% (149/154)	98.0% (96/98)	94.6% (53/56)

IGTP-Haiti	Standardized case definitions for TB			
FujiLAM	Unlikely TB	Unconfirmed TB	TB confirmed	Total
Negative	3	47	2	52
Positive	1	3	3	7
Total	4	50	5	59

CONCLUSIONS

- Promising methods, biomarkers and signatures are coming to allow accurate diagnosis and prognosis.
- It is critical to validate in different geographic settings and to translate the test to a near-patient platform.
- **Mandatory good communication between all the professionals involved in TB control and patient associations and communities.**

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