FIND

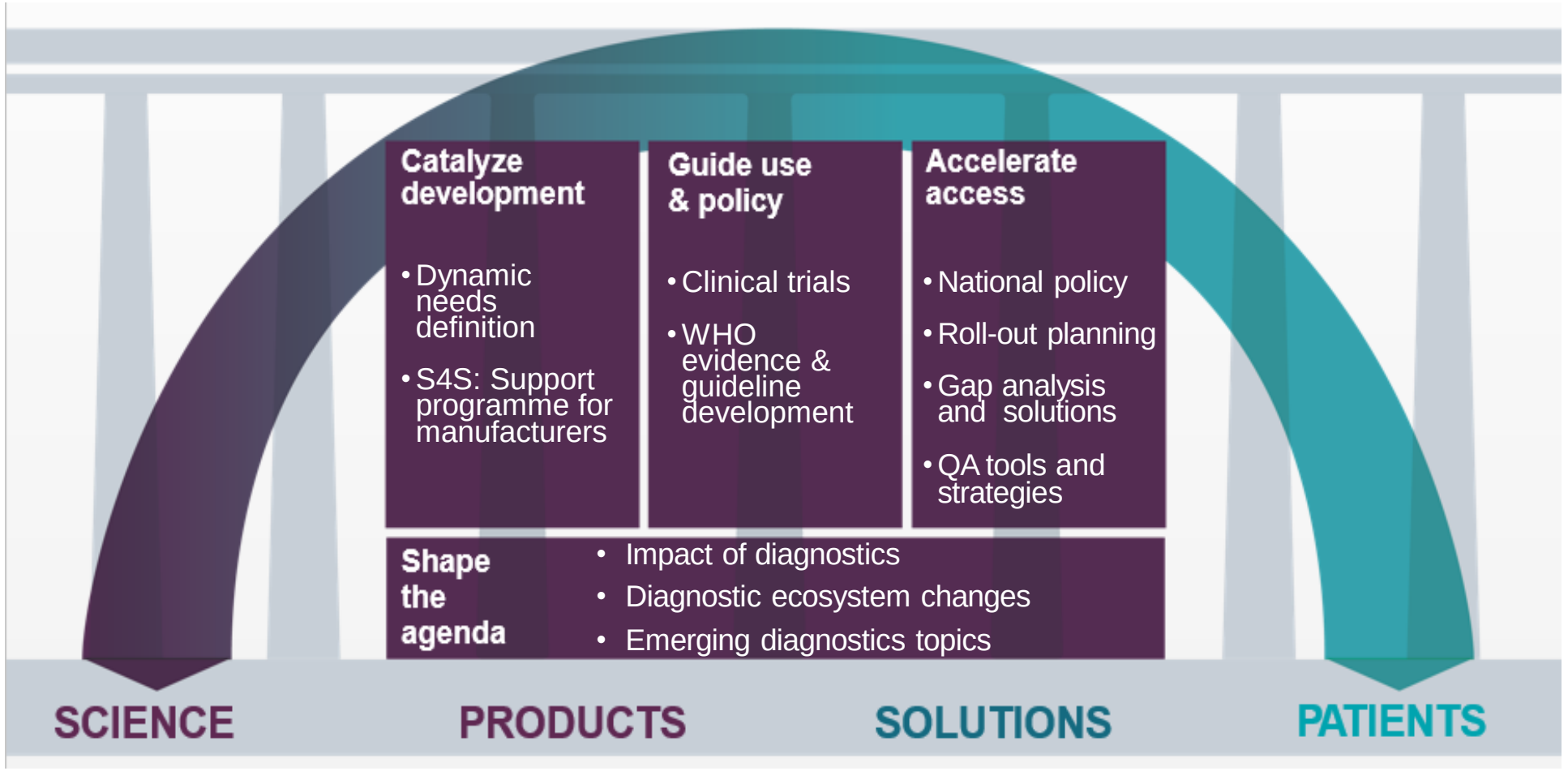
Because diagnosis matters

The diagnostic fever landscape and ongoing studies (at FIND)

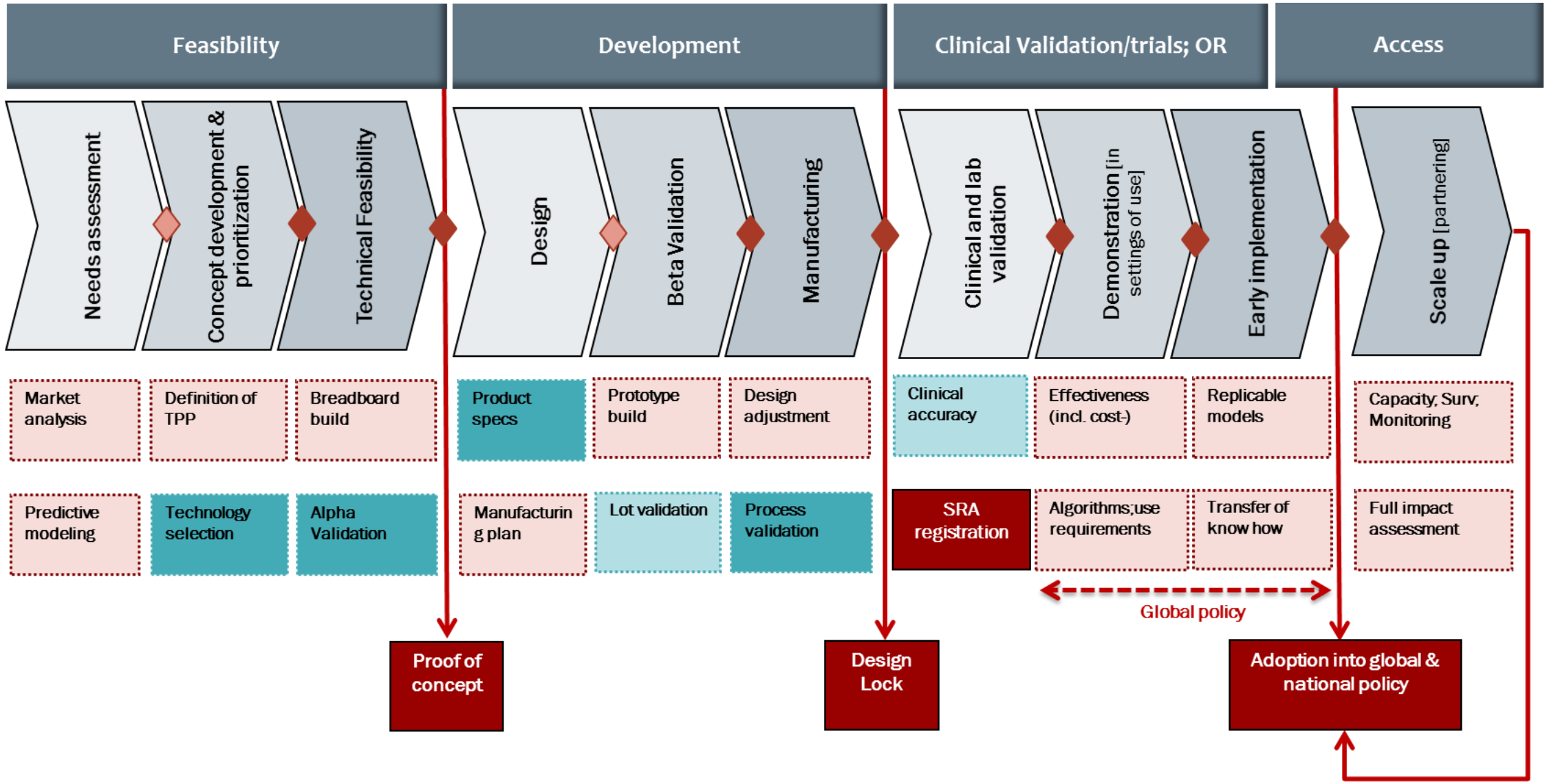
Sabine Dittrich, Head of Malaria
& Fever Program

Febrile Illness meeting, Annecy, 21 January2019

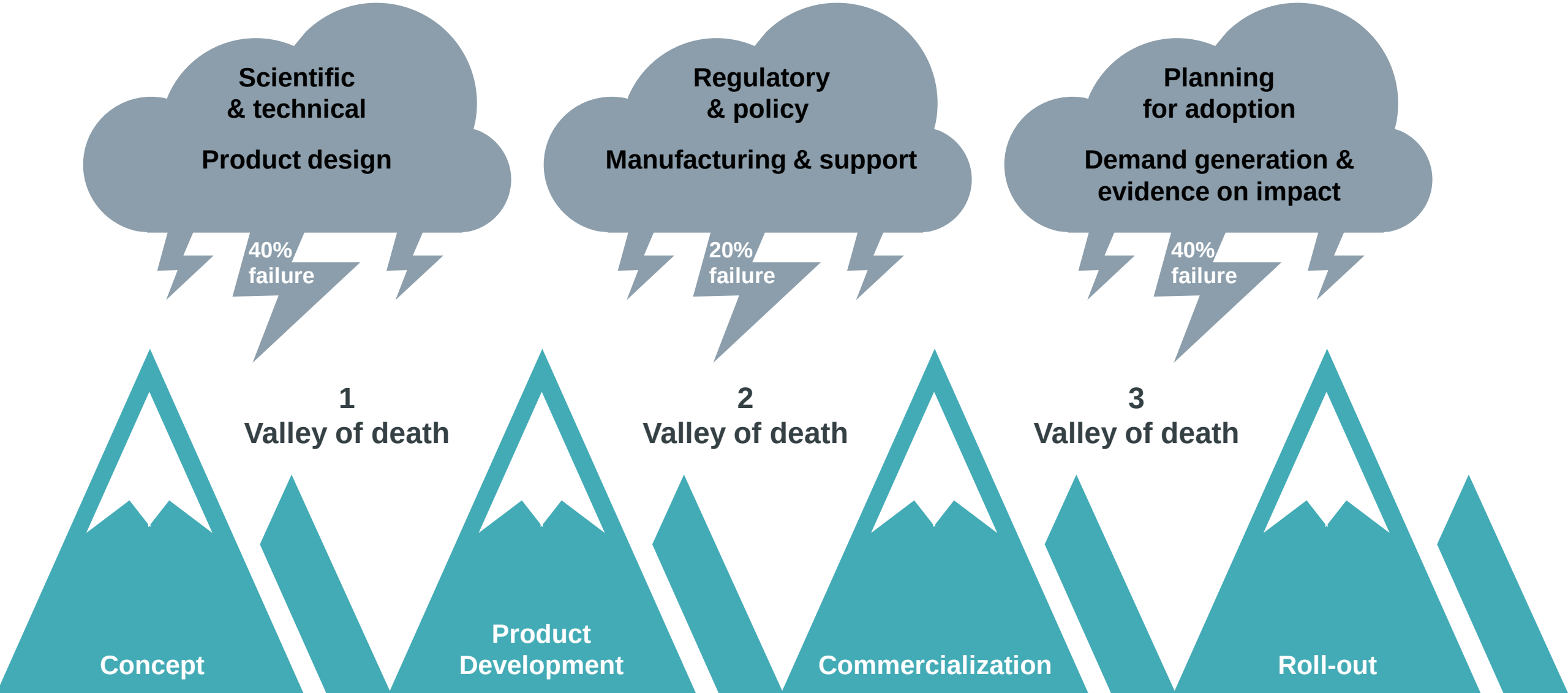
Turning complex diagnostic challenges into simple solutions to transform lives



Development pipeline to bring any diagnostic to the market



Three ‘valleys of death’ confront diagnostics innovators



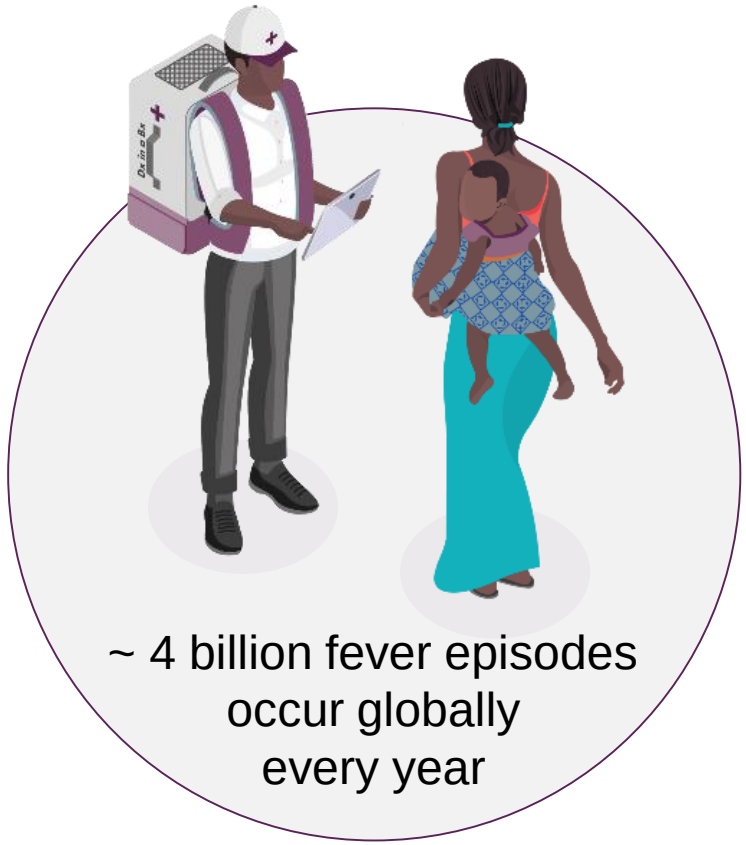
A holistic approach to ensure everybody receives the right treatment

Refer to hospital

- severity
- ID & DST

Provide malaria drugs

- ACT
- Radical cure



~ 4 billion fever episodes occur globally every year

Provide supporting care

- Nutrition
- antipyretics

Send home to rest

Provide antibiotics

- Doxycycline
- Broad spectrum

*based on global fever estimate models (CHAI)

Unmet and Prioritized Needs (TPPs)

Community health worker	Health post	Local Clinics/ Microscopy centres	District hospital	Reference centre

* Triage test to differentiate bacterial from non-bacterial infections

* Simplified blood culture

* Multiplex and multi-analyte platform

* eHealth&Dx Solutions

Highly sensitive malaria RDTs

P. vivax serology to enable radical cure

Improved *P. vivax* point of care testing

Non-malarial projects

Malaria/Fever cross cutting

Malaria-only projects

Triage tests to differentiate bacterial from non-bacterial infections

Support dedicated product development and demonstrate impact

Beyond malaria: Malaria negative patients will benefit from a simple triage test to guide treatment beyond malaria to inform antibiotic prescribing and care decisions.

- Develop target product profiles (TPPs)
- Validation of host biomarkers in LMICs to understand utility in context of common co-morbidities
- Develop sample biorepository to help assay development
- Support/advise diagnostic product development of:
  - Multiplexed biomarker assay (BD)
  - Malaria + CRP assay (SD Biosensor)
- Understand the utility of using a biomarker test and how it impacts prescription and outcome

Target Product Profile for a Diagnostic Assay to Differentiate between Bacterial and Non-Bacterial Infections and Reduce Antimicrobial Overuse in Resource-Limited Settings: An Expert Consensus

Sabine Dittrich[1]*, Birkneh Tilahun Tadesse[1,2,3], Francis Moussy[4], Arlene Chua[5], Anna Zorzet[6], Thomas Tängdén[6], David L. Dolinger[1,4,5], Anne-Laure Page[7], John A. Crump[8,9,10], Valerie D'Acremont[11,12], Quique Bassat[13,14], Yoel Lubell[15,16], Paul N. Newton[15,17], Norbert Heinrich[18], Timothy J. Rodwell[1], Iveth J. González[1]

Biomarker feasibility study – an example

Study size and analysis plans based on priority needs identified in TPP

- Sample size of 1500 patients calculated based on the following assumptions

Inclusion criteria

- ✓ Presenting at the outpatient department
- ✓ Aged between 2 and 65 years
- ✓ Presenting with a fever >38°C (oral or ear Tre) or >37.5°C (axillary or forehead Tre)
- ✓ Fever duration < 7 days
- ✓ Signed written informed consent for study participation
- ✓ Willingness to have study follow up visit, approx. 2 to 3 weeks after enrolment

Exclusion criteria

- X Being severely ill
- X Unwillingness to have blood samples collected
- X Unwillingness to have an HIV test performed

Table 2. Acceptable and desired target product profile characteristics focused on the scope of the test, as defined by an expert consensus process 2015–16.

Characteristic	Acceptable ("must have")	Desired ("would like")	Reference
Goal	Rapid, biomarker-based testing to differentiate between bacterial and non-bacterial infections to guide antimicrobial treatment.[a]		Expert consensus
Target population	Children with non-severe, non-malarial acute fever presenting at health facilities.[b,c,d]	Total febrile population (including neonates) presenting with fever.[b,c,d]	[4,35]
Target level of health system	Level 1, passive case finding	Level 0	[37]
Target user	Healthcare worker	Trained lay person	[38]
Price of individual test (Ex works)	5 USD[e]	<1 USD[e]	Expert consensus
Analytical sensitivity/Limit of detection	Limit of detection should be such that it allows clinically relevant performance as defined below		Expert consensus
Diagnostic sensitivity to differentiate between bacterial and non-bacterial infections	≥90%	≥95%	Expert consensus
Diagnostic specificity to differentiate between bacterial and non-bacterial infections	≥80%	≥90%	Expert consensus

Dittrich *et. al* 2016

Biomarker feasibility study: New and old biomarkers being evaluated alongside

Biomarker selection based on the outcome of the landscape from 2016

- C-reactive protein (CRP) (ELISA)
- Procalcitonin (PCT) (ELISA)
- Human Neutrophil Lipocalin (HNL) (ELISA)
- FebriDx (MxA + CRP) (RDT)
- Heparin-Binding Protein (HBP) (ELISA)
- Chitinase 3-like-1 protein (CH13L1) (ELISA)

Kapasi AJ, et al. 2016, PLoS One

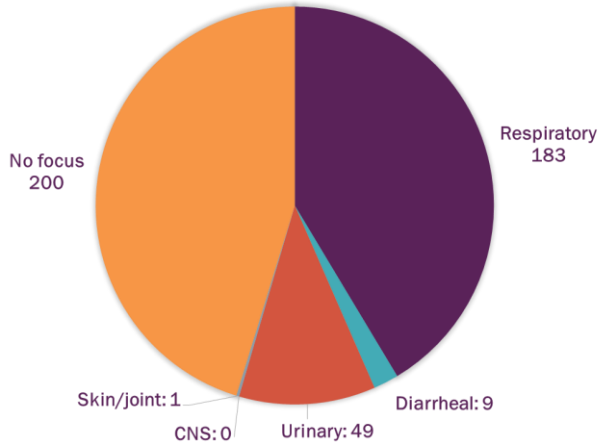
NOTE: Additional markers being tested as they become available

Brief overview of some laboratory test results

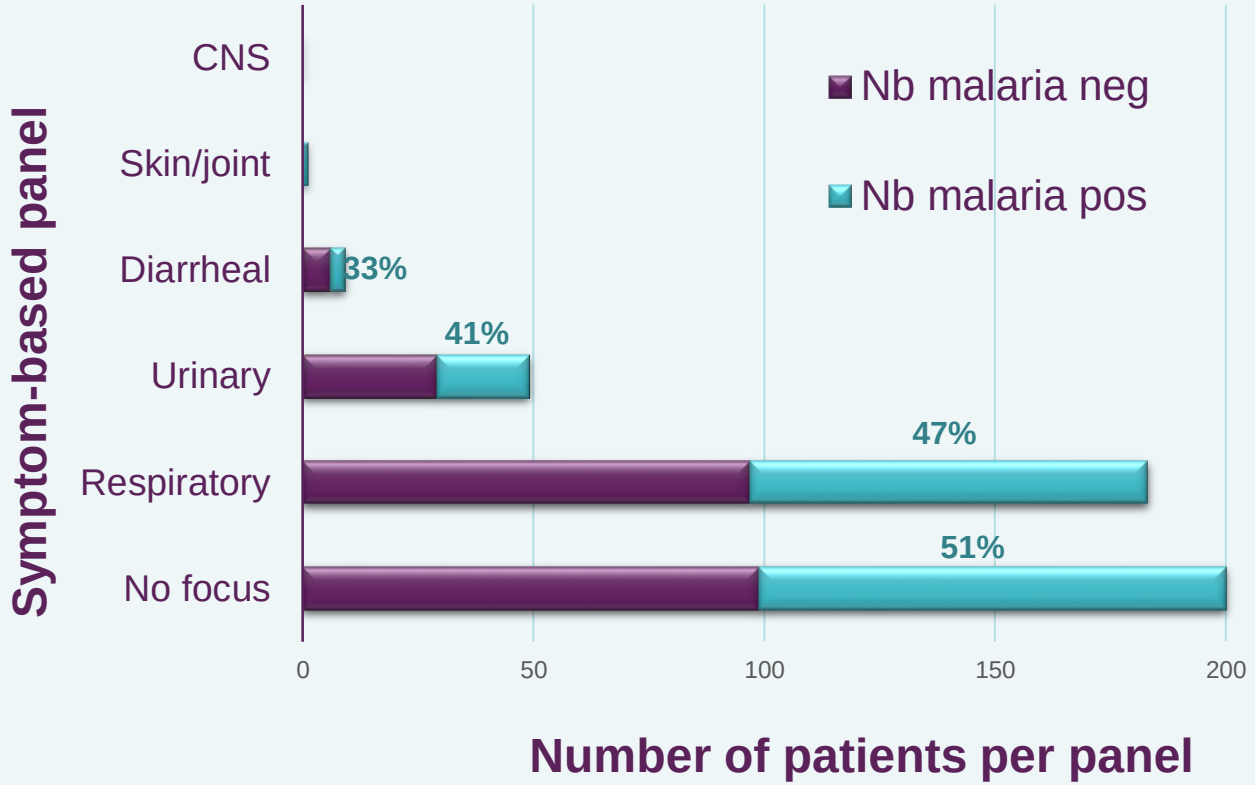
Lab tests performed on all 424 patients

Positive results	Nb of patients	% patients
Malaria RDT	206	49%
HIV RDTs	20	5%
Typhoid RDT	147	35%
Blood culture	10	2%

Number of patients per symptom-based panel



Distribution of malaria RDT positives per syndromic panel



Current status of the biobank to support future test development

Biobanking for future test development

- Samples from **1,000 patients** from Malawi stored in biorepository in the US
- Over **20,000 samples** including serum, plasma, urine, whole blood and PAXgene samples
- Biobanked samples soon available* to partners through FIND website

*contact us already if you are interested to move your innovation forward (Camille.Escadafal@finddx.org)

Multiplex and multi-analyte platform

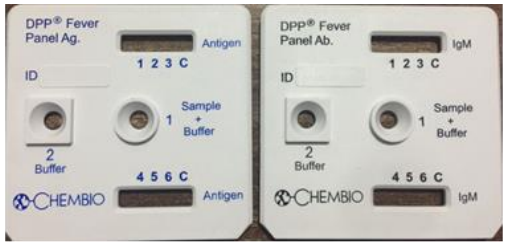
Support dedicated product development and demonstrate impact

- Retrospectively mapping the causes of fever to understand priorities and gaps

- Develop target product profiles (TPPs)
  - Multiplex platform to support fever management of severe patients (MSF/FIND/WHO)

- Partnerships to support development:
  - Multiplexed RDT for 8 pathogens aiming to guide treatment decisions particularly in SEA (Chembio)
  - Multiplex fever diagnostic program in partnership with MSF and WHO (https://www.finddx.org/target-product-profiles/)

- Evaluation and late stage product development support by enabling testing in the field with multiple partners (e.g. Johns Hopkins, MORU, Menzies, NIMR)



Antigen Detection
- ChikV
- **Malaria pLDH**
- *B. pseudomallei*
- ZikV
- **Malaria HRPII**
- Dengue

IgM Detection
- ZikV
- ChikV
- DenV
- Murine typhus
- Scrub typhus
- Leptospira spp.

Sever patients in the hospital with bloodstream infections
Support dedicated product development and demonstrate impact

- Develop target product profiles (TPPs)
  - Simplified blood culture tool (Dailey *et al.* 2019)

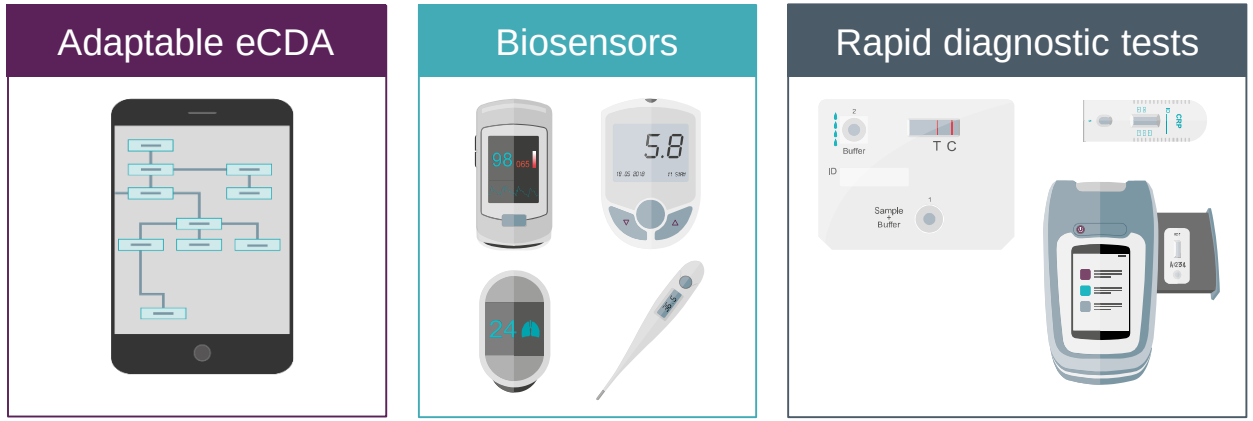
- Feasibility study with Specific Technology

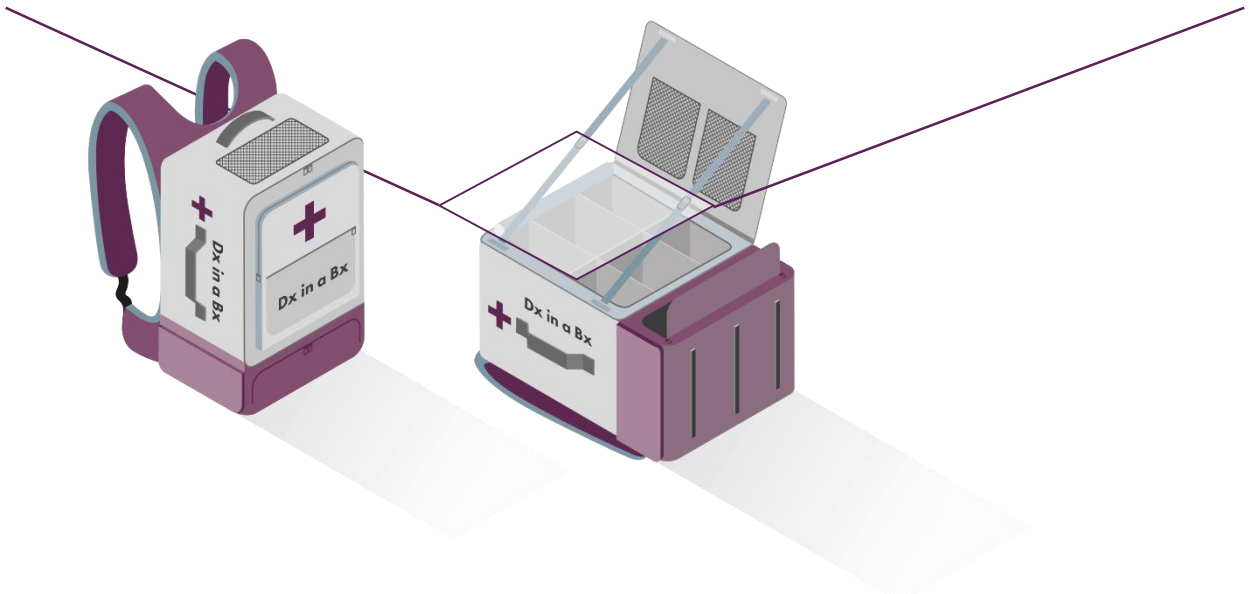
- Understand the utility of using a rapid pathogen ID test for positive blood cultures in a pilot in a tertiary hospital in Botswana (Gabarone, Princess Marina Hospital)
  - RCT to understand impact on treatment decision if a simpler blood culture ID system is used
  - Arms: Rapid diagnostic vs standard of care
  - Sample size 800 patients (400 in each arm)
  - Recruitment ongoing (data expected in Q4 2019)

McMaster University

Truly integrated fever management by augmenting all diagnostic efforts and linking them to electronic clinical guidance tools

Combining all our efforts in product development, connectivity and guidance tools to form a “Dx in a Bx”.





- Develop target product profiles (TPPs)
- Understanding the landscape and business models required for sustainability
- Feasibility studies with multiple partners to ensure dx/eHealth link

Demonstration projects to facilitate access of existing tools

Clinical trials to show the impact of already existing diagnostic tests to improve targeting of treatment

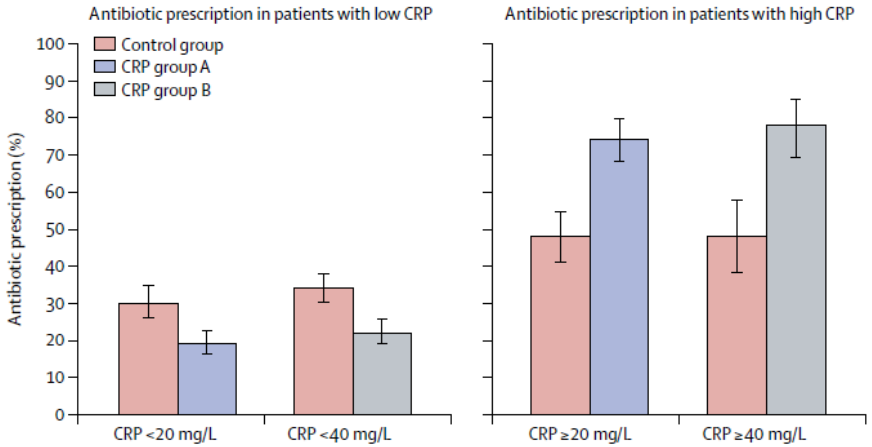
- Use of CRP in acute respiratory patients in Thailand (Althaus et a. 2018)
- Large scale demonstration study to show the impact of CRP on prescribing in Vietnam (ongoing work with MORU)
- Rapid pathogen identification study in Botswana (recruitment ongoing)

Providing solutions not only diagnostics

- Multiple ongoing connectivity projects aiming to improve data usage of fever/AMR diagnostic
- WHO / FIND collaboration to shape agenda for the use of eHealth tools used with diagnostic tools

Dx use accelerator: a collection of projects to change policy: **partner with FIND! check: www.finddx.org**

Market shaping activities to understand roll-out requirements for non-donor driven markets



(Althaus et al. 2018)

Acknowledgements

Team

Sabine Dittrich
Head of Program

Camille Escadafal
Scientific Officer

Karell Pelle
eHealth Scientific Officer

Xavier Ding
Team Lead Malaria

Sandra Incardona
Scientific Officer

Seda Yerlikaya
Scientific Officer

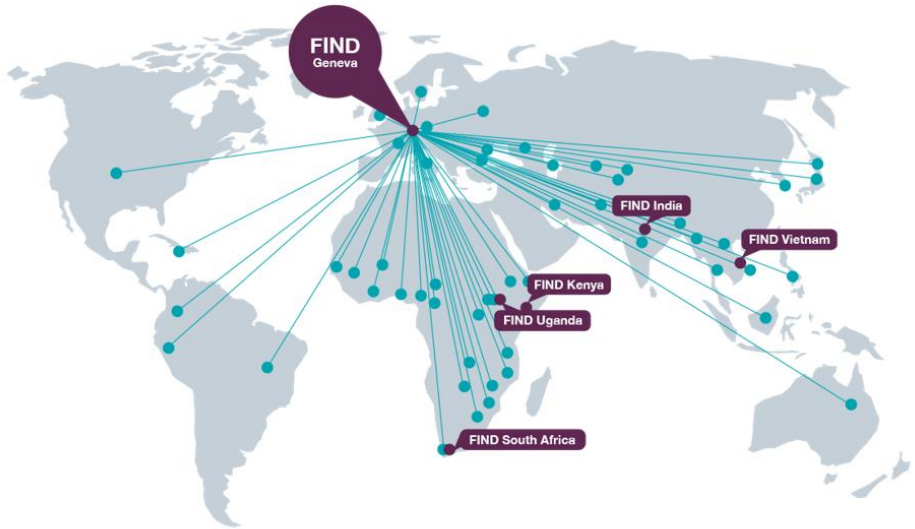
Maïda Vandendorpe
Project Manager &
Program Coordinator

Natalia Cubilla
Administrative Assistant

Sonia Arafa
Scientific Officer

Leticia Fernandez
Scientific Officer

Partners



Universities and research institutes	Industry	Government/ multilateral agencies	Advocacy	Clinical trial sites	Implementing partners
• 44 partners	• 46 partners	• 35 partners	• 2 partners	• 32 partners	• 26 partners

MEIRU
Malawi Epidemiology and Intervention Research Unit

INI
Instituto Nacional de Infectologia Evandro Chagas

cermel

CHUV

wellcome trust MORU Tropical Health Network

menzies school of health research

McMaster University

(Main program) Funders

Unitaid
Innovation in Global Health

UKaid
from the British people

BILL & MELINDA GATES foundation

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra
Swiss Agency for Development and Cooperation SDC

Australian Government
Department of Foreign Affairs and Trade

Ministry of Foreign Affairs of the Netherlands

fondation BOTNAR

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS